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N-heterocyclic Carbene Copper-Catalyzed Carboxylation of Alkynes with Carbon Dioxide

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Tiivistelmä/Referat – Abstract

Copper complexes are versatile catalysts for different fixations of carbon dioxide. Copper-catalyzed carboxylations of unsaturated hydrocarbons with CO_2 provide access to valuable carboxylic acids. Generally, the formation of Cu-C species from the substrate and the catalyst is followed by carbon dioxide insertion across the Cu-C bond which produces copper carboxylate RCOO-Cu via C-C bond formation. Moreover, copper complexes can undergo transmetallation with less-nucleophilic organoboron reagents to afford Cu-C species. Copper-catalyzed reductive carboxylations of C-C unsaturated bonds with CO_2 entail hydrogenative, alkylative and heterocarboxylation methodologies.

This thesis elaborates a protocol for the N-heterocyclic carbene copper (I)-catalyzed synthesis of carboxylic acids from alkynes with carbon dioxide. The main interest lies in a regioselective hydrocarboxylation of alkynes catalyzed by NHC-copper hydrides and copper-catalyzed carboxylation of alkylboranes with CO_2. The literature review focuses on the catalytic activity of N-heterocyclic copper (I) complexes in organometallic chemistry, especially within a range of reductive carboxylation reactions. Alkynes insert readily into the copper hydride bond constituting C-Cu species prior to the CO_2 insertion. The regioselectivity of this carboxylation reaction derives from the *syn* addition of Cu-H species to the alkyne. Correspondingly, the alkylboranes can be carboxylized in a regiospecific fashion due to the regioselective manner of the initial hydroboration.

In the experimental part, two different catalytic hydrocarboxylation pathways were carried out with *in situ*-copper (I) catalysts. The use of mild base additive CsF was necessary for the catalyst formation. The first pathway was catalyzed by a NHC-copper(I)-hydride complex in the presence of hydrosilane as the reducing agent. In the second pathway, a tandem hydroboration carboxylation sequence was utilized, catalyzed by copper(I) fluoride species. Both pathways furnished carboxylic acids from terminal and internal alkynes.

Avainsanat – Nyckelord – Keywords

Carbon dioxide, Copper, N-heterocyclic carbenes, Alkynes, Carboxylation, Catalysis

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List of abbreviations

Ar	aryl
cod	1,5-Cyclooctadiene
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DMF	dimethylformamide
dppb	1,4-bis(diphenylphosphino)butane
dppp	1,3-bis(diphenylphosphino)propane
dppz	dipyridophenanzine
Et_2O	diethyl ether
EtOAc	ethyl acetate
h	hours
Hex	hexane
ICy	cyclohexyl imidazolin-2-ylidine ligand
IMes	1,3,5-trimethyl imidazolin-2-ylidine ligand
i-Bu	isobutyl
i-Pr	isopropyl
*i*Pr	2,6-diisopropyl group
IPr	2,6-isopropyl imidazolin-2-ylidine ligand
Mes	1,3,5-trimethylphenyl group
Me	methyl
MeCN	acetonitrile
MeOK	potassium metoxide

Mes	mesityl
min	minutes
n-Pr	*n*-propyl
NMR	nuclear magnetic resonance
OMe	methoxy group
pin	pinacolate
rt	room temperature
*t*Bu	*tert*-butyl
*t*BuOK	potassium *tert*-butoxide
*t*BuONa	sodium *tert*-butoxide
TBDPSO	*tert*-Butyldiphenylsilyl
THF	tetrahydrofuran
TMDS	1,1,3,3, tetramethyldisiloxane
TMS	trimethylsilyl

I. Literature review

1. Introduction

This thesis consists of a literature review and an experimental section, which was performed in the laboratory. The literature part deals with the catalytic activity of N-heterocyclic copper(I) complexes in organometallic chemistry, especially within the reductive carboxylation reactions of alkynes with carbon dioxide. The experimental part begins with the synthesis of various NHC-copper(I) complexes. Afterwards, the focus will be on the NHC-copper hydride-catalyzed hydrocarboxylations of alkynes with CO_2 and hydrocarboxylation via organoboranes.

1.1 Carbon dioxide

1.1.1 General

Carbon dioxide (CO_2) has a growing feasibility in organic chemistry as a source of carbon. It is used as a readily available, mild, green, inexpensive, recyclable and nontoxic C_1 synthons for different transformations. As a drawback, since the carbon is in the most oxidized state (+IV), the molecule is chemically inert. In addition to this, CO_2 shows considerable thermodynamic stability among various transformations. Therefore, high-energy co-reagents are required for coupling reactions with CO_2 in most cases. The formation of new C-C bonds can take place prevalently in the presence of strong carbon nucleophiles, such as organolithium and Grignard reagents, which are intolerant towards many useful functionalities. Consequently, further investigation is needed for efficient and mild coupling reactions between less nucleophilic substrates and CO_2 for formation of C-C bonds.[1,2,3]

1.1.2 Reactivity

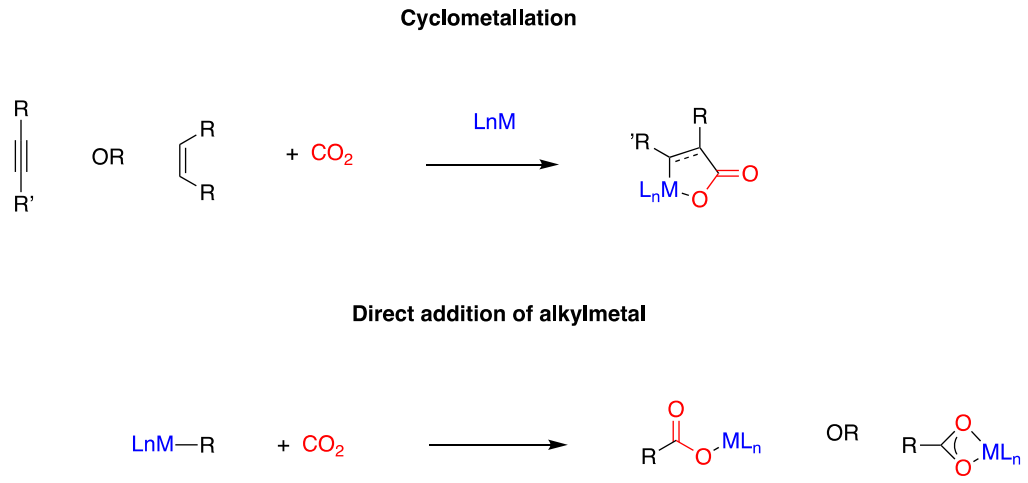
The CO_2 molecule has 16 valence electrons and a linear configuration containing two polar and equal C=O bonds. The carbonyl carbon atom is an electrophilic center while both oxygens show a weak nucleophilicity. This weak nucleophilicity is ruled over by the electrophilicity of the CO_2 molecule, leading to an overall electrophilic character of the molecule.[1,4]

The incorporation of CO_2 into synthetically useful chemicals can be roughly divided into two main pathways:1) Direct incorporation of CO_2 into the substrate molecule via carbonation or carboxylation without a need of external energy and 2) the catalytic reduction of CO_2. The first pathway produces carbonyl moieties bearing carbamates, carbonates and ureas, in which carbon retains its oxidation state of +IV. The catalytic reduction of CO_2 affords for example CO, CH_3OH, CH_4 and CH_2O. Efficient metal catalysts are required for most of these transformations.[2,3,7]

1.1.3 Carbon dioxide insertion

CO_2 insertion into the highly reactive transition metal-element (M-E) bond is a versatile approach for CO_2 activation. The insertion can take place into the bond between carbon and another element, such as C, H, N, O, P, Si and B. The CO_2 insertion is initiated by a nucleophilic attack of E at the electrophilic carbonyl carbon. This process may be assisted by the interaction between the lone electron pair of the oxygen atom and the metal atom center.[4,5,6]

An oxidative coupling between CO_2 and an unsaturated substrate at the transition metal center is another pathway for CO_2 transformations. The unsaturated substrate is typically olefin, alkyne, aldehyde or imine, which are forming electron rich and low valent complexes with the transition metals and the CO_2. There are two main types of C-C bond formation mechanisms with CO_2 (Scheme 1). The properties of the transition metal and substrate determine which further compounds can be formed from the CO_2 incorporated intermediate.[5,6,7] Cyclometallation usually takes place with π-unsaturated compounds. A direct addition of alkyl or alkenylmetal complex to CO_2 is the other pathway.[8]



Scheme 1. C-C bond formation mechanisms of CO_2.[4,9]

1.2 Reductive carboxylations with carbon dioxide

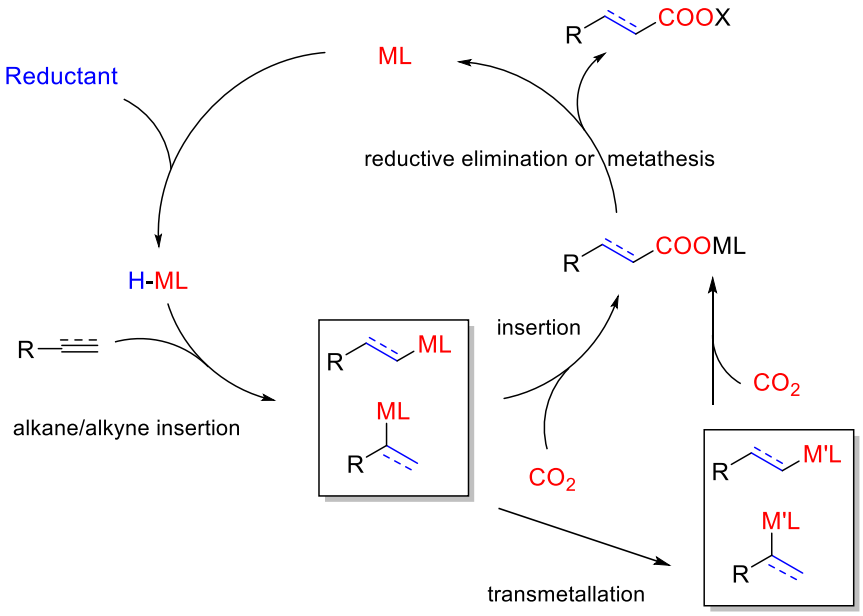
1.2.1 General

The ubiquitous carboxylic acids are useful synthons in organic transformations as well as applicable substrates for medicinal uses. For instance, an industrially important application is the direct CO_2 incorporation to salicylic acid derivatives, and the acrylic acid manufacture from ethene and CO_2, which is currently under development.

Reductive carboxylation methodology is a versatile approach for the carboxylation of unsaturated structures. The unsaturated C-C double- or triple bonds serve as coveted substrates in the presence of various transition metal catalysts providing diverse carboxylative transformations. For instance, catalytic hydrocarboxylation of abundant olefins and alkynes with CO_2 generates extensively utilized α,β-unsaturated carboxylic acids in an atom economic pathway. The scope of the reductive carboxylations of unsaturated hydrocarbons with CO_2 entail hydrogenative, alkylative and arylative carboxylations.[6,7,8] In contrast, the carboxylation of unsaturated substrates including carbon-hetero bonds are far less investigated. The simultaneous addition of heteroatom

functionality and carboxyl moiety to the unsaturated C-C bond enables the generation of highly applicable multifunctionalized products via heterocarboxylation.[7,8]

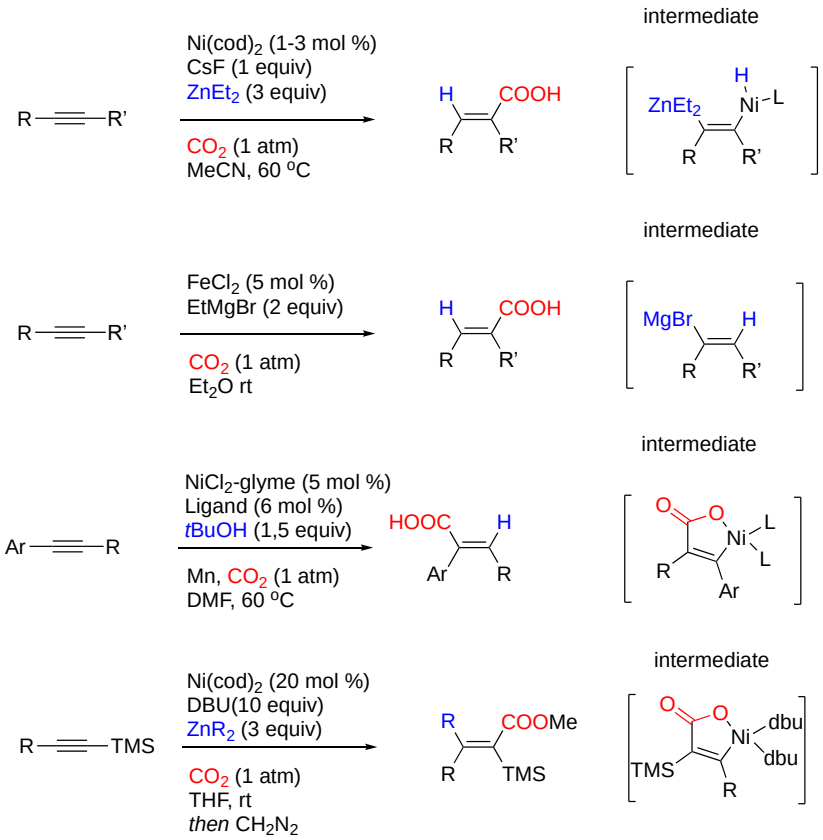
A typical reductive carboxylation pathway consists of the nucleophilic addition of a metal-catalyst to the unsaturated C-C bond, and subsequent CO_2 insertion across the M-C bond shown in Scheme 2. The CO_2 insertion into the M-C bond is a very significant step due to the new C-C bond formation. The resulting carboxylato complex (R-COO-M) enables the release of the carboxylic product and the regeneration of the catalytically active species completing the catalytic cycle. Both organometallic reagents and nucleophiles can be employed in a regio- and stereoselective manner among the reactions. However, the functional group tolerance limitations and high air sensitiviness of common reducing agents, such as organozinc reagents have evoked a demand for more compatible reagents.[6,7,8,9]



Scheme 2. Common mechanistic rationale for reductive carboxylation via direct CO_2 insertion into alkyl- or alkenyl metal complex.[9]

1.2.2 Carboxylation of alkynes with CO_2

The coupling of alkynes in the presence of CO_2 for the synthesis of pyrones was one of the first well-known carboxylation reactions. Nickel and cobalt-catalyzed cycloaddition of CO_2 generated cyclic products in low yields. The mechanistical studies of these cycloadditions revealed the nickelactone intermediates, which could lead to the straightforward synthesis of acrylic acid derivatives via subsequent protonolysis or reaction with alkyl electrophiles.[5,7,8] The regioselectivity among the hydrocarboxylation of terminal alkynes was later controlled via thermodynamic and kinetic factors of the nickelactone intermediate, as well as the steric properties of the ligands employed. The electronic effects of the ligands were utilized for the regiospecific carboxylations of internal alkynes. The first carboxylation transformations were performed in a stoichiometric manner. Later, catalytic amounts of the organometals allowed for more efficient reactions. Both α- and β-carboxylic acids could be obtained with the catalyst and ligand fine-tuning. The nickelactone-mediated carboxylations have shown wide applicability among different transformations.[7,8,9] Alternatively, simple alcohols, hydrosilanes and even water have been employed as the hydrogen sources and for enhancement of the functional group tolerance. The electronic and steric influence of the ligands play a key role when it comes to the regioselectivity. Other transition metal catalysts used for analogous transformations entail iron, zirconium, cobalt and copper complexes, which is more closely addressed in this literature review. Scheme 3 shows selected reductive carboxylation pathways for alkynes.[7,8]



Scheme 3. Selected examples of reductive carboxylation of alkynes.

In addition, the reductive carboxylation methodology can be extended to the carboxylation of ynamides, double carboxylation of internal alkynes and synthesis of lactone derivatives. Alternative pathways include the carboxylation of organoboron reagents, such as alkylboranes and acetylic boronates produced from alkynes and organoboron reagents.[7]

1.3 N-heterocyclic carbenes

1.3.1 Structure and properties

N-heterocyclic carbenes (NHCs) are common ligands used in organic and organometallic chemistry, which have an increasing number of applications. The electron-rich NHCs have a strong σ-donor ability and they form robust complexes with

metal centers. This is due to the electron donation ability of the free electron pair from the carbenic carbon to the metal orbital. Therefore, the metal-ligand bond can be considered as a dative bond. NHC ligands have the electron configuration of a singlet ground state, separating them from other carbenes, such as Schrock and Fischer type carbenes. The lone pair of the carbon atom is sp^2-hybridized while the p_π-orbital remains unoccupied. The cyclic azole ring has a significant electronic stabilizing effect, which arises from the π-donation of the nitrogen atoms to the empty p_π-orbital of the carbenic carbon. Simultaneously the nitrogen atoms have a withdrawing σ-electron effect. In addition, the cyclic structure amplifies the singlet state due to the bent sp^2-character of the carbenic carbon. Bulky substituents on the nitrogen atom are used to stabilize the structure kinetically, one of the more common structure of a resonance stabilized NHC ligand is shown in Figure 1.[10,11,]

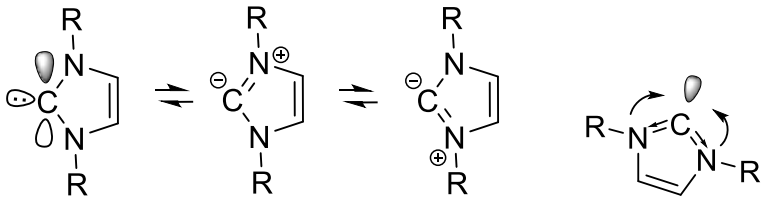


Figure 1. Structure of an N-heterocyclic carbene.

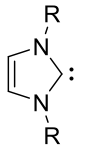
1.3.2 NHC-metal complexes

NHC ligands form robust bonds with transition metal centers with both high and low valency. The NHC-metal complexes show high thermal and oxidative durability and it is possible to facile tune the steric and electronic nature of the catalyst. The strong σ-donation of the carbenic carbon to the metal center represents the predominant bonding mode in the NHC-metal complexes. The p-orbital of the carbene also accepts electron density from the metal via π-back bonding as stated above. Consequently, the bond has a double bond character, which results in short metal-ligand bond lengths. On the other hand, NHCs have a stronger σ-donating ability than other σ-donating ligands, such as

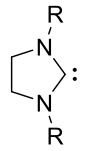
phosphines. The strength of the NHC-metal bond is therefore thermodynamically greater than in phosphine-metal bonds, due to higher dissociation energies.[10,11,12,31,32]

In contrast to the sp^3-hybridized phosphines, the cone angle is larger for the NHC ligands. The nitrogen substituents of the carbene are directed towards the metal center while the the azole ring is oriented outwards from the metal. Despite the bulky structure of the NHC-complex, the rotation around the M-C bond decreases this sterical hindrance. With these attributes NHCs are spectator ligands that render both stabilizing and activating effect on the central metal. This convenient fine-tuning of the carbene through substituents, backbone and the ring structure, enables a considerable enhancement in the selectivity and efficiency of the transformations achieved with the NHC-metal catalysts. In addition, the increase in catalytic activity can be achieved via the electronic and steric impact of the carbene ligand on the metal.[10,11,12,31,32]

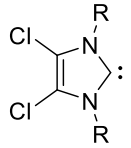
NHC-copper species serve as efficient catalysts to functionalize a wide scope of substrates, such as carbonyls, olefins, allenes and alkynes. In particularly, the NHC-copper catalyzed carboxylation transformations with CO_2 show high potential. The five-membered NHCs, such as imidazol-2-ylidines (**1a**, **1b**, **1c)** and imidazolin-2-ylidines (**2a**, **2b)** form the biggest class of these ligands and they are very compatible with copper(I) species to generate versatile catalyst complexes, such as **4**, **5** and **6**.[13,14] The following sections of this review will elaborate on the properties and applications of the NHCs shown in Figure 2.



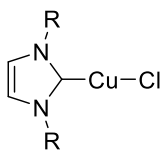
R = Mes IMes **1a**
R = 2,6-(iPr)$_2$C$_6$H$_3$ IPr **1b**
R = cyclohexyl ICy **1c**



R = Mes SIMes **2a**
R = 2,6-(iPr)$_2$C$_6$H$_3$ SIPr **2b**



R = 2,6-(iPr)$_2$C$_6$H$_3$ Cl_2IPr **3**



R = Mes (IMes)CuCl **4**
R = 2,6-(iPr)$_2$C$_6$H$_3$ (IPr)CuCl **5**
R = cyclohexyl (ICy)CuCl **6**

Figure 2. The structure of imidazol- and imidazoline-2-ylidine ligands.[10]

2. Copper hydride catalysts

2.1. Phosphine ligated copper hydrides

Copper(I) hydrides serve as mild and selective reductants.[15,16] Phosphines were the first ligands used to form a copper hydride complex in order to catalyze the reduction of activated olefins.[15,17] Stryker's reagent, $[CuHPPh_3]_6$ was one of the first commonly known copper hydride complexes used for the regioselective conjugate reduction of multiple α,β-unsaturated carbonyls with a good functional group tolerance (Figure 3).[17]

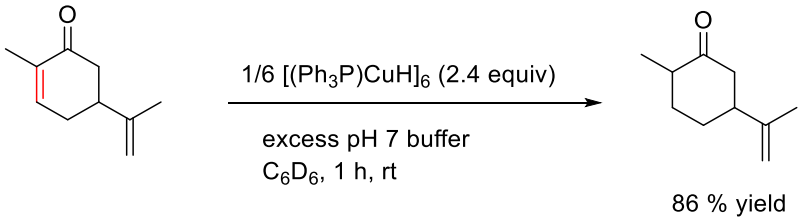


Figure 3. Reduction of α,β-unsaturated carbonyl compounds with Stryker's reagent.

As a drawback, the complex showed inadequate reactivity towards more congested structures and unactivated double bonds. The catalytical efficiency was enhanced when hydrosilanes were introduced as hydrid sources replacing the initially used H_2 gas.[18,19,20] Through ligand modification enantioselective asymmetric reductions were enabled for α,β-unsaturated esters. An efficient reduction was achieved by chiral bidentate phosphine **7** ligated copper hydrides (Figure 4).[21] An efficient copper hydride complex used for selective conjugate reductions of various sterically demanding carbonyls was obtained with 1,2-bis(diphenylphosphino)benzene ligand **8** allowing the use of only 0.1 mol % of the ligand loading.[8] The selectivity of the conjugate reductions can be

achieved with the use of a specific phosphine ligand.[22,23,24] For α,β-unsaturated ketones 1,4-reduction predominates in the presence of phenylphosphines, such as **8**.[22] In comparison, enantioselective 1,2-reduction can be achieved with biphenyl bisphosphine ligands, such as **9**.[25] In addition, the use of biphosphines enables asymmetric hydrosilylation of arylketones.[24,25,26]

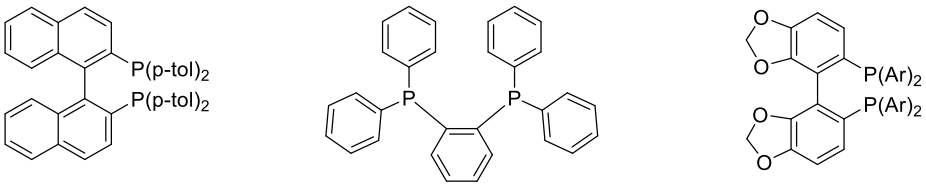
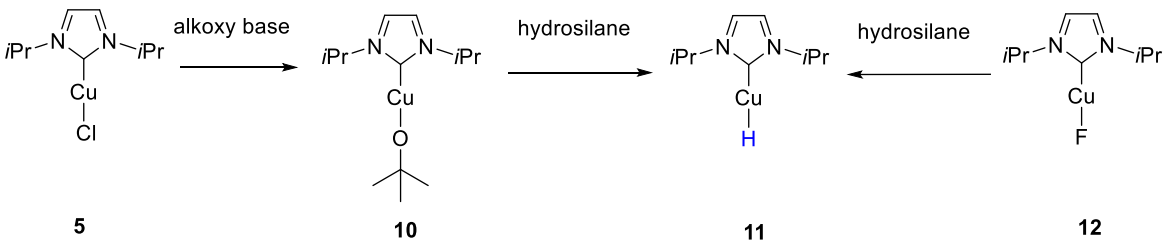


Figure 4. Different phosphine ligands for the copper hydride-catalyzed conjugate reduction of carbonyls.

2.2 NHC-Copper hydrides

N-heterocyclic copper hydrides (as **11** in Scheme 4) serve as chemoselective reducing agents.[27,28,29,30] The electron rich NHC ligands **1-3** provide an increased reactivity due to their high electron donating ability as discussed above.[31,32] This strong σ-donation of the carbene ligand to the copper center enables great catalytical reactivity of the copper hydride **11.**[27,30] The copper-ligand interaction also decreases the potential ligand dissociation.[31,32]

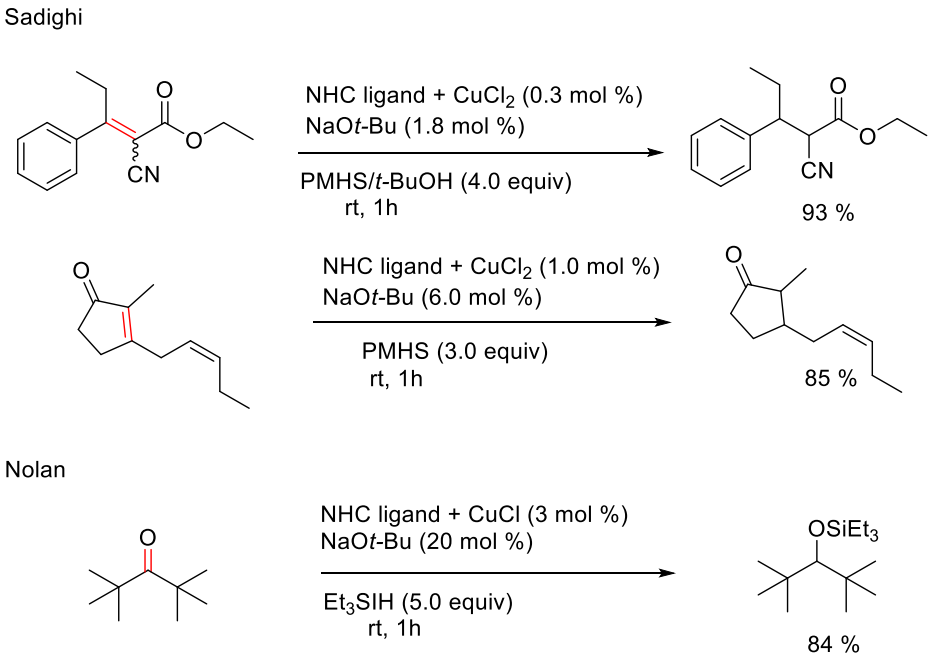


Scheme 4. Generation of (NHC)copper hydride complex.

Stoichiometric amounts of hydrosilanes, such as (EtO_3SiH), (Et_3SiH), PMHS, TMDS, Ph_2SiH_2 and $PhMe_2SiH$ provide economical and green hydride sources for the formation of **11**.[19,20] Alternative proton sources, such as boranes (Et_2BH) and stannanes (Bu_3SnH) have also shown applicability in different reductions with copper species, but they are commonly used with phosphine-ligated copper hydrides.[33,34]

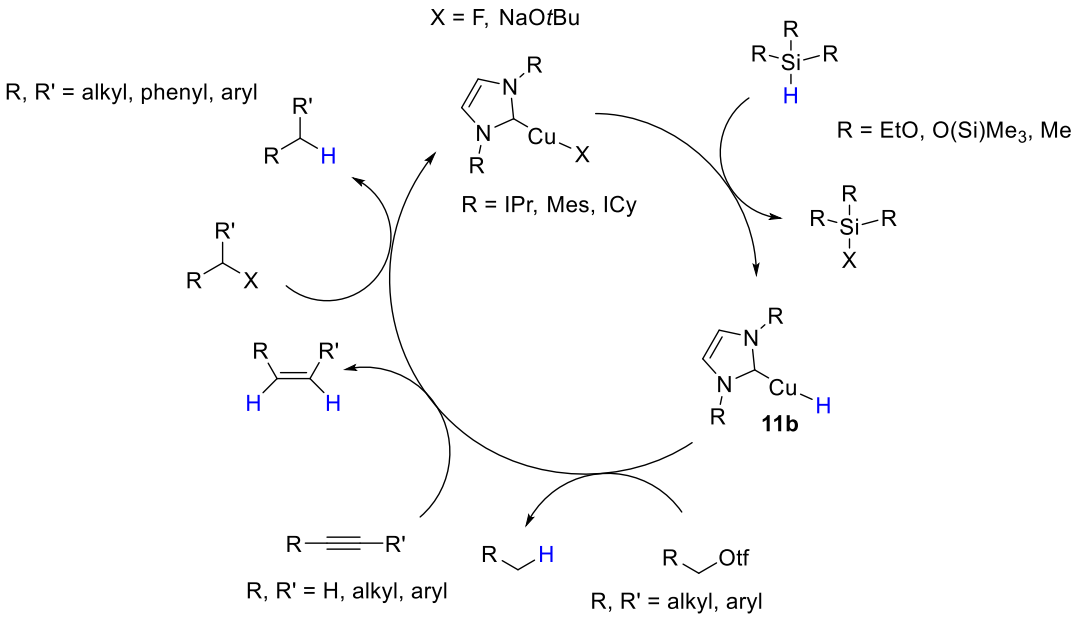
The highly active copper hydride, as **11,** can be obtained when an alkoxy base, such as sodium *tert*-butoxide is introduced to copper species **5** and forming first an NHC-copper alkoxide intermediate **10**. In a subsequent step the σ-bond metathesis between **10** and a hydrosilane generates **11** *in-situ*.[27,28,29,35,36,37] Correspondingly, NHC-copper fluoride analogues of **12** produce the desired hydride **11** directly when reacted with the silane.[36,37] The *in-situ* produced **11** allows the use of a very low catalytic loading down to 0.1 mol % catalyst for a vast number of transformations.[28]

NHCs are highly functional group tolerating ligands among various conjugate reductions of α,β-unsaturated. The use of **11** allows mild reduction conditions and high selectivity of carbonyl substrates resulting in high yields, concluding more demanding hindered and functionlized ketones as well as substituted cyclic enones and esters (Scheme 5).[27,28,35,38]



Scheme 5. NHC-Copper hydride-catalyzed 1,4-reduction of substituted esters and cyclic enones.[28,35]

In addition to the diverse conjugate reductions of unsaturated double bonds, the catalytic reductions with analogues of **11** entail: semi-reduction of alkynes to Z-olefins, deoxygenation of primary alcohols, reduction of primary alkyl sulfonates and alkyl halides and hydrosilylation of carbonyls.[27,38] Scheme 6 depicts the catalyzed reduction of alkynes, triflates and halides catalyzed by copper hydrides.[38,39]

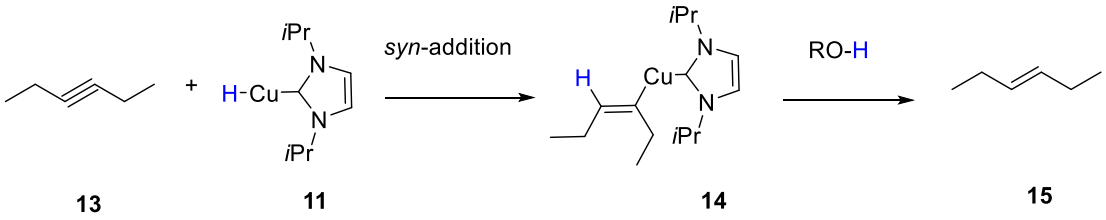


Scheme 6. (NHC)Copper hydride formation and catalytic reduction of alkynes triflates and halides.[39]

The use of NHC-copper hydrides as the reducing agents simultaneously with alcohols which are delivering the proton source, offers a regiospecific approach for semireduction of alkynes.[39,41] This approach is superior to for example the use of the more common Lindlar catalyst with hydrogen, due to the chemoselective nature of NHC-copper species. Hydride **11** is non-reactive towards simple olefins thus avoiding the possible over reduction to alkanes.[39,40,41]

Remarkable stereoselectivity can be achieved among the hydrocupration step due to the considerable *syn*-addition of **11** to the triple bond of simple internal alkyne like **13** to generate copper alkenyl intermediate **14**. Therefore, the desired (Z) products, such as **15**

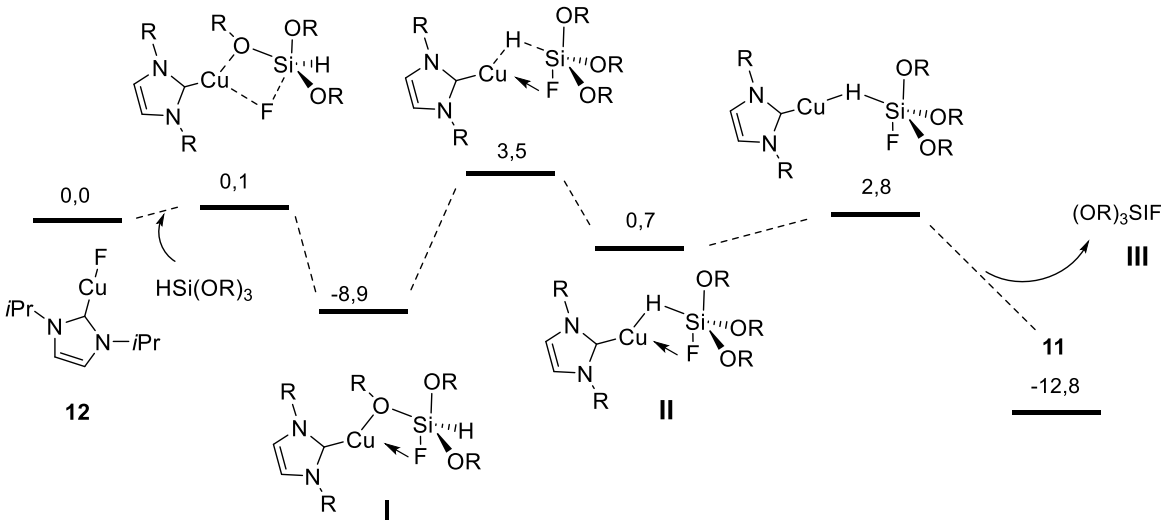
are favoured, minimalizing the formation of the mixture of the stereoisomers (Scheme 7).[39,41]



Scheme 7. Semi-reduction of internal alkynes with (NHC)CuH and alcohol.[39,41]

The stoichiometric reaction between NHC-copper fluorides like **12** and the hydrosilane was studied computationally by Lin *et al*.[28] The generation of corresponding hydrides (Scheme 8) turned out to be very favorable in both kinetic and thermodynamic perspectives. The total formation energy was calculated to be -12,8 kcal/mol indicating an exothermic reaction.[42]

In the depicted reaction mechanism, the fluoride first migrates from the copper center into the silicon producing intermediate **(I).** Subsequently an agostic silicon-hydrogen ligated intermediate **II** takes place simultaneously cleaving the copper-oxygen bond. The generation of fluorosilane **III** releases finally **11**. Overall**,** most of the steps had a very low or almost no energy barriers indicating a rapid generation of **11**.[28]



Scheme 8. Formation of NHC-copper hydride. Free formation energies are given in kcal/mol.[42]

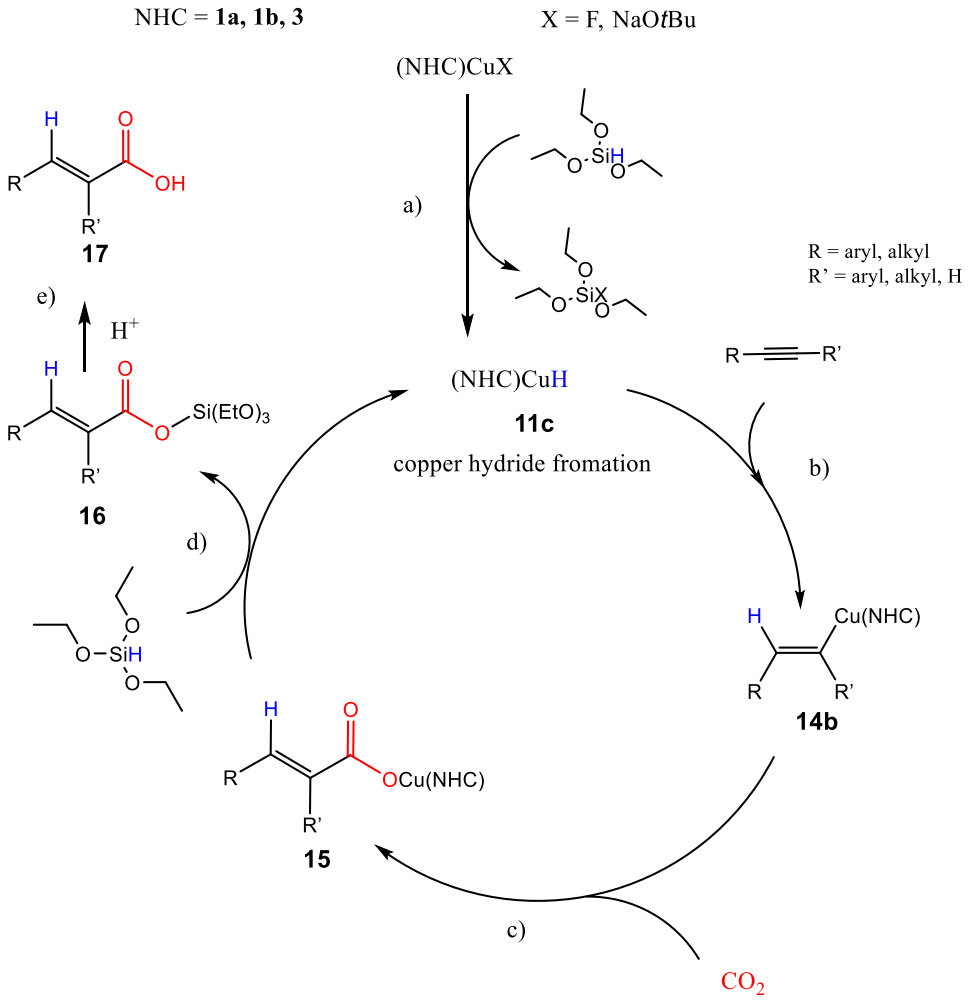
2.3 (NHC)copper hydride-catalyzed hydrocarboxylation of alkynes

The reduction of unactivated alkynes proceeds via hydrocupration by the copper hydride **11** producing an NHC-copper alkenyl intermediate **14** (Scheme 7)**.**[39,41] Fuji *et al* discovered that the formation of analogues of **14** offers further possibility for a hydrocarboxylation step.[36] Instead of a subsequent protonation to the corresponding (Z)-olefin, CO_2 is introduced yielding a hydrocarboxylized product. The hydrocarboxylation pathway of internal alkynes catalyzed by NHC-copper hydrides is a versatile approach for synthesis of synthetically important 1,2-disubstituted carboxylic acids.[36]

The mild and easily to handled hydrosilanes make the catalytic pathway notably greener in comparison to the strong and moisture sensitive reducing agents, such as $ZnEt_2$ and $AlEt_3$ commonly used for hydrocarboxylations of alkynes.[43] On the other hand, the use of silanes expose the alkynes, as well as CO_2 to possible hydrosilylation. In the optimized reaction conditions however, the interfering hydrosilylation can be overcome.[36,42]

Hydrocarboxylation of alkynes in the presence of CO_2 can be performed with various copper complexes. Hydrosilanes, such as triethoxysilane and polymethylhydrosilane

(PMHS) are successfully employed as the hydride sources. Scheme 9 shows the proposed reaction mechanism.[36,39,42]



Scheme 9. Copper(I) catalyzed hydrocarboxylation of alkynes with CO_2 using hydrosilanes. a) formation of the CuH catalyst, b) insertion of alkyne, c) insertion of CO_2, d) formation of carboxylate intermediate and catalyst regeneration, e) work up and final carboxylic acid formation.[36,42]

In the proposed cycle (Scheme 9) the catalytically active copper hydride **11c** is generated from the precatalyst derivates of **10** or **12,** when introduced to the hydrosilane**,** similarly as presented earlier in Scheme 4.[28,29,34,36] In the following step alkenyl intermediate **14b** is generated as a consequence of *syn*-hydrocupration of the starting alkyne and **11c**.[39,41] The CO_2 insertion produces a copper carboxylato complex **15** which undergoes a σ-bond

metathesis with excess hydrosilane. This results in the regeneration of **11c** back to the catalytic cycle and formation of silylated carboxylate **16.** An aqueous work up finally releases the desired product **17** with *E*-stereochemistry.[36,42] Effective hydrocarboxylation for internal alkynes were obtained giving α,β-unsaturated carboxylic acids in considerably high yields.[36]

NHC-copper catalysts like **4** and **5** having chloride in their structure usually require the use of *tert*-butoxides to make them more Lewis basic, in order to form **11c** with the hydrosilane.[28,39,35]

Fujihara *et al* developed new efficient fluorinated NHC-copper catalyst analogues of **12** with ligands **1a**, **1b** and **3**. The less Lewis acidic fluoride readily forms **11c** with the hydrosilane in the absence of *tert*-butoxides. The ligand choice plays also a key role to enhance the regioselectivity of the products. For instance, the electron-rich chlorinated ligand **3** increased the reactivity of internal aryl substrates bearing alkyl substituents.[36]

The substituent effects for the regioselectivity were remarkable. Bulkier alkyl substituents showed considerably better regioselectivity than methyl substituents, improving the formation of single *E*-regioisomers. Selected examples of different alkynes compatible for the reaction with corresponding yields are shown in Figure 5.[36]

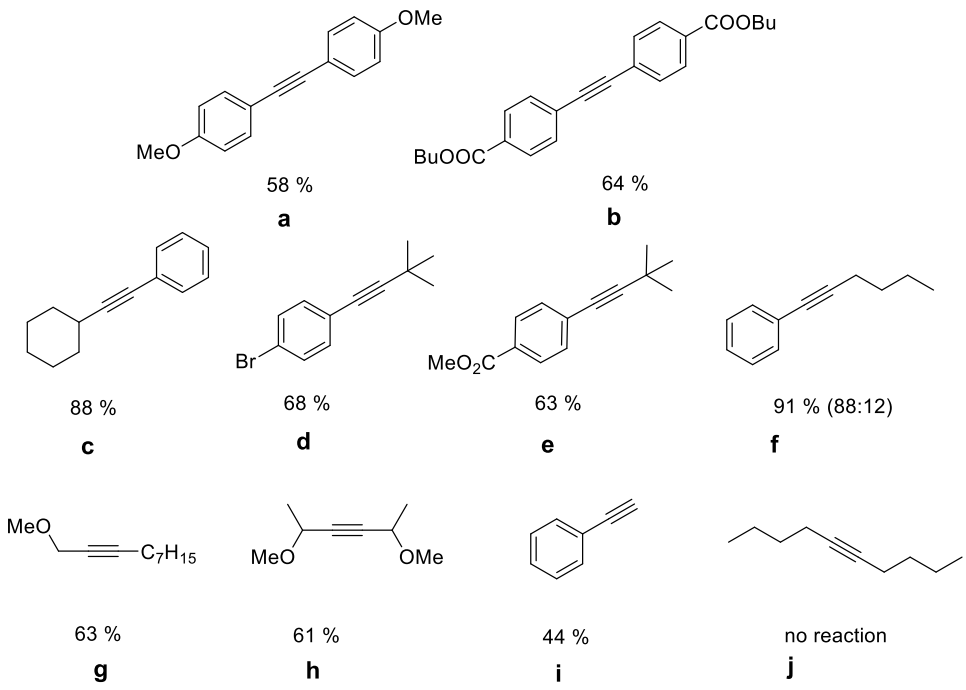


Figure 5. Substrate scope for the hydrocarboxylation of alkynes.[36]

It can be seen (Figure 4) that both symmetrical electron rich **(a)** and electron deficient **(b)** aryl substituents show good functionality giving relatively high yields.[36]

Aryl halide substituted **(d)** as well as alkoxy substituted alkynes **(a,g h)** are also tolerated. *Tert*-butoxy and cyclohexyl functionalities overcome the formation of the mixture of regiomers producing single isomers in good yields **(c, d, e).** Aliphatic simple internal alkynes show poor reactivity or no reactivity at all against the hydride species **11c,** leading to a low formation of **14b**. For example, 5-decyne **(j)** decomposes in the reaction conditions. Methoxy group **(g)** seems to increase the yields, indicating that the ether functionalities in the starting alkyne most probably have a strong coordination to the copper center.[36] The methodology is not fully extended to terminal alkynes **(i)** due to a significant formation of the reduced olefin as a side product.

The hydrocupration reaction producing **14b** is an irreversible reaction with a high free energy barrier.[42] Therefore it is the plausible rate determining step for the hydrocarboxylation methodology. On the other hand, the subsequent CO_2 insertion into the copper alkenyl complex **14b** is heterogeneous and thus slow at room temperature. Elevated temperatures are needed for the reaction to proceed and therefore the formation of complex **15** is from the experimental point of view supposed to be the rate-determining step.[36,42] In summary, it is clear that the copper hydride **11c** plays a key role in the reaction.

In comparison to the nickel catalyzed carboxylations, the copper catalyzed reactions are slower, but the carboxylic group can be added to the more nucleophilic substituent side with the copper catalysts. Moreover, Cu and Ni –catalyzed reactions provide comparable yields. The Ni-catalyzed alkyne hydrocarboxylation method however, clearly favours the electron rich aryl substrates making the copper catalyst more diverse for this purpose (compare to Scheme 3).[8,9,43,44]

3. Reductive carboxylation via organoboranes

3.1 Hydroboration of unsaturated hydrocarbons

Boron-carbon bonds have an important role in organic synthesis due to their unique reactivity.[45,53,55,] Organoboranes and boronates are applicable in the formation of new carnon-carbon and carbon-hetero bonds.[53,55] Organoboron reagents are abundant and less moisture sensitive in comparison with organolithium and Grignard reagents.[45,47] Hydroboration of double and triple bonds are widely reported including both terminal and internal structures.[45,46,50,60,61,64] The substrate scope entails for instance, alkyl, aryl, silyl and propargyl substituents.[45] 9-boracyclo(3.3.1)nonane **18** and bis(pinacolato)diboron **19** are the most versatile diboranes used for this purpose (Figure 5).[45,49,50,55]

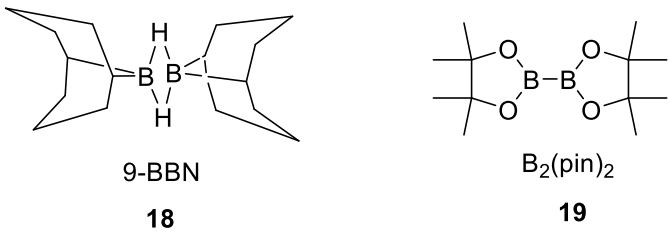


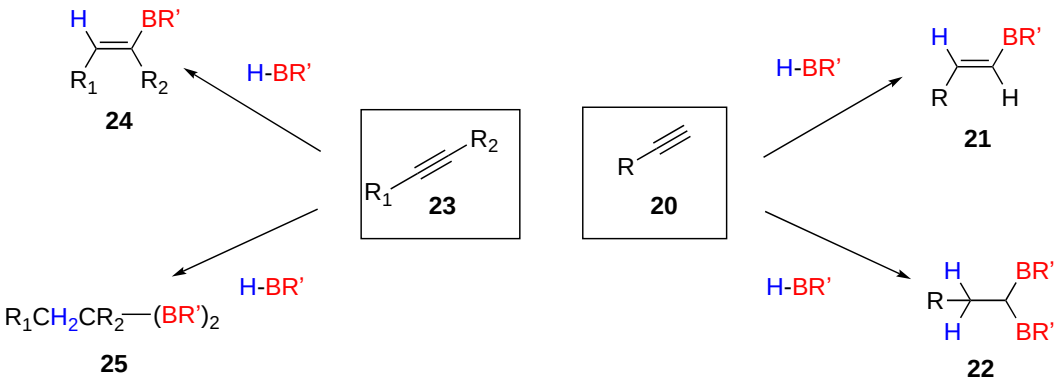
Figure 6. Structures of 9-BBN and B_2pin_2 dimers.

Synthetic routes for preparation of monoborylalkanes, 1,1-diborylalkanes, 1,2-diborylalkanes and even 1,1,1-triborylalkanes have been reported.[45,46] Hydroboration of alkynes furnish mono and dihydroborated products respectively. The diborylated products are considerable intermediates for C-C bond formations via cross-coupling reactions, such as Suzuki-Miyaura.[45,46,55] Regio- and stereoselectivity of the desired hydroborated products can be controlled by using suitable catalyst system. For instance, Cu, Ni, Pt and Rh catalysts are reported.[45,46,48,53]

3.2 Hydroboration of alkynes

3.2.1 Metal free hydroboration

The hydroboration of alkynes provides an excellent pathway for further synthetic transformations via the generation of alkenylboranes and alkylboranes. Thus, a metal free protonolysis of alkenylboranes enables a straightforward synthesis of the semi-reduction product analogues of **15** (Scheme 7).[38,51] Treatment of both internal (Scheme 10a) and terminal (Scheme 10b) alkynes **20** and **23** with diborane reagents leads to the formation of mono- (**21**, **24**) and dihydroboration (**22**, **25**) products depending on the amount of diborane.[45,49,50] The monohydroboration of terminal alkyne **20** with diborane reagent affords the product **21** which exclusively shows *trans*-isomerism of the vinyl protons due to the *syn*-addition of the B-H bond. In addition, the hydroboration is regioslective due to the addition of the borane at the terminal position.[51,52] The monoaddition of borane to the internal alkyne **23** also gives *syn*-product **24**. The diborylated products **22** and **25** arise from sequential hydroboration of the alkenylboranes **21** and **24**.[49,50]

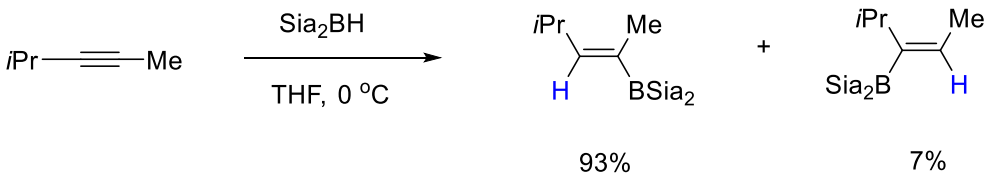


Scheme 10. Hydroboration of internal (a) and terminal (b) alkynes.[45,49,50]

The introduction of 9-BBN dimer **18** to the solution with alkyne generates essentially β-vinyl-9-BBN products (analogues of **21** and **24**) or *gem*-dibora products (analogues of **22** and **25**). The molar ratio of alkyne and organoborane has a direct influence on the formation of the primary product.[50] This is due to a competition reaction between the initially formed monoborylated product and the unreacted alkyne for the remaining borane. Equimolar rection between **18** and terminal alkynes generate quantitative amounts

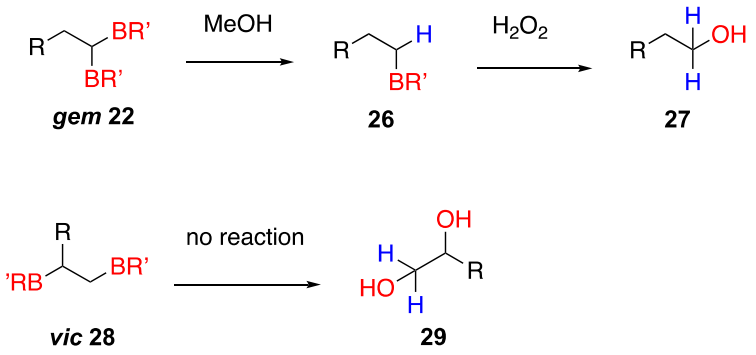
of dihydroborated products. Thus, a stoichiometric reaction (2 equiv of 9-BBN) results in a complete uptake of the diborane in 6 hours at rt, affording 1,1-diborylalkanes such as **22**.[50] Nevertheless, an excess of alkyne can be used to disable the double hydroboration. A significant regioselective control can be achieved with two equivalents of alkyne and one equivalent of **18** producing mainly the desired monoborylated products with yields of 90-100 %.[50] In comparison, the reaction between equimolar quantities of **18** and internal alkynes stops after the completion of the monoaddition stage. However, the excess of **18** furnish corresponding dibora derivatives also from internal alkynes in quantitative yields. The hydroboration of internal substrates is however strongly affected by the steric factors of the substituents.[51]

The major hydroboration product tends to be the least sterically hindered.[49,50] Disubstituted alkynes with unsymmetrical substituents form both regioisomers, however boron will be added to the carbon on the less hindered side of the substrate (Scheme 11).[51,52] A use of alkyldiboranes, such as bulky dicyclohexylborane (Chx_2BH) and disiamylborane (Sia_2BH) produce only monohydroborated products due to their sterical hindrance.[51]



Scheme 11. Monohydroboration with sterically hindered boranes.

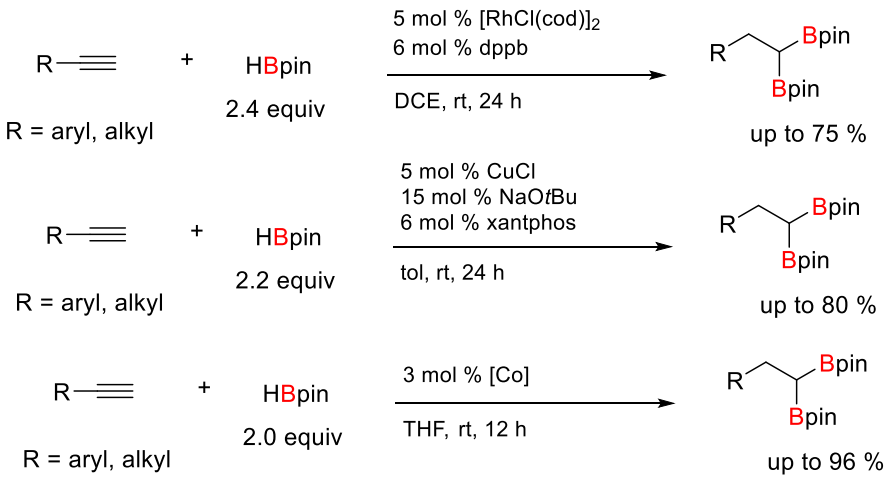
The dibora derivatives (**22** and **25**) were established to show *gem*-form according to the study of Brown *et al*.[50] The protonolysis of 1,1-diborylalkane **22** to corresponding β-alkyl-9-BBN intermediate **26** followed by an oxidation with hydrogen peroxide was investigated and only primary alcohols, such as **27** were obtained (Scheme 12). Internal substrates showed similar reactivity. In general, the corresponding reaction of *vicinal* substrate **28** would lead to the formation of glycols **29**. The absence of any glycols indicates however, that the double hydroboration of alkynes proceeds exclusively to the generation of *gem*-dibora products **22**.[50]



Scheme 12. Protonolysis and oxidation of 1,1-diboryl adducts.

3.2.2 Transition metal catalyzed hydroboration of terminal alkynes

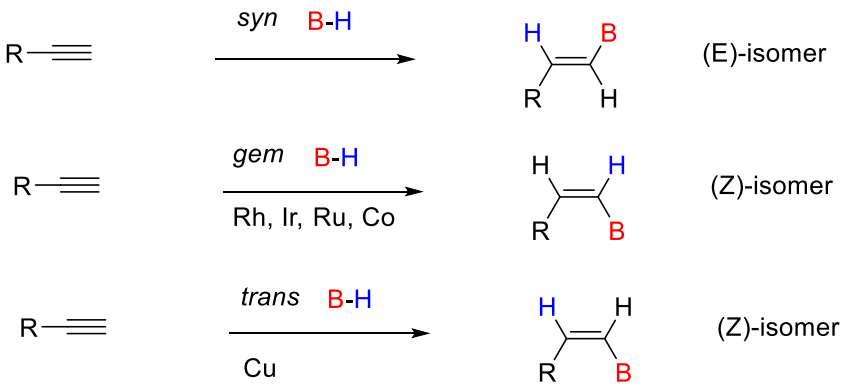
Transition metal complexes can be utilized to achieve regioselective control and efficiency over double hydroboration of terminal alkynes. Various approaches for the regioselective synthesis of a 1,1-diboronate esters from different terminal alkynes with two equivalents of pinacolborane and a transition metal catalysts are reported. A wide scope of different aryl and alkyl substituents are tolerated in these hydroboration reactions. In most cases, base additives or hydride sources are required for activation. The reactions can be carried out at room temperatures and the complete consumption of the borane is achieved in 12-24 hours. An overview of these reactions is shown in Scheme 13.[48,49,52]



Scheme 13. Transition metal catalyzed sequential hydroboration of terminal alkynes.[48,49,52]

Most of the above reactions produce undesired monoborylated products or 1,2-diboryl products but with the use of suitable catalyts systems the amount of these side products can be minimized.[48,49,52]

In addition, the stereospecific control over the synthesis of alkenylboranes can be achieved with transition metal catalysts. The treatment of terminal alkynes with equimolar amount of diborane yields β-vinyl products with E-isomerism in metal-free conditions as discussed above (Scheme 10), but also Z-isomers can be obtained selectively using Rh, Ru, Ir, Co and Cu-catalysts. The formation of Z-products takes place via *gem*-addition of the B-H bond. Even *trans*-hydroboration is enabled leading to the *cis*-isomerism of the vinyl protons. However, monoborylated alkylboranes are formed as side products in most cases. The scope of different transition metal-catalyzed monohydroborations of terminal alkynes is shown in Scheme 14.[53,54]



Scheme 14. Transition metal-catalyzed hydroboration pathways of terminal alkynes affording alkenylboranes.[53]

As a conclusion of this chapter, the hydroborated products can be readily protonolysed to corresponding alkenes and they can perform 1,2 and 1,4-additions to form carbonyls.[50] In contrast, diborated derivatives can form secondary alkyl boranes with alkyl halides.[51] Transition metal reagents, especially copper undergo readily transmetallation with alkylboranes **21** and **22** to produce alkyl or vinylcopper species which enable further

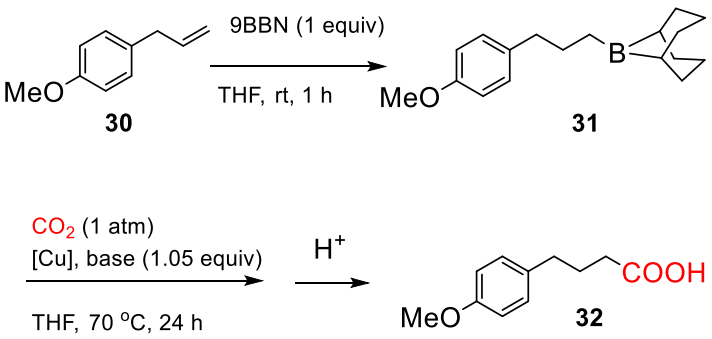
functionalization possibilities. For instance, carboxylations can be performed in the presence of suitable base.[50,57] The various analogues of **22** and **25** can afford malonic acid products via carboxylation with CO_2, which will be further discussed in this review.[57,64]

3.3 NHC-copper-catalyzed hydrocarboxylation of organoboranes

3.3.1 Tandem hydroboration carboxylation of terminal olefins

To further understand, the mechanism of the tandem hydroboration carboxylation of alkynes, an intriguing option is to look at the reactivity of olefins.

Organoboranes are readily available and functional group-compatible reagents. Carboxylation of aryl- and alkenylboronic esters catalyzed by various transition-metal catalysts are commonly known and reported.[58,59] Hydroboration is a versatile method for preparation of alkylboranes as stated earlier in the hydroboration section (Scheme 10). A reductive carboxylation of unsaturated hydrocarbons with CO_2 via alkylboranes is a promising approach into the synthesis of various carboxylic acids and their derivatives.[60,61,64,67,68]



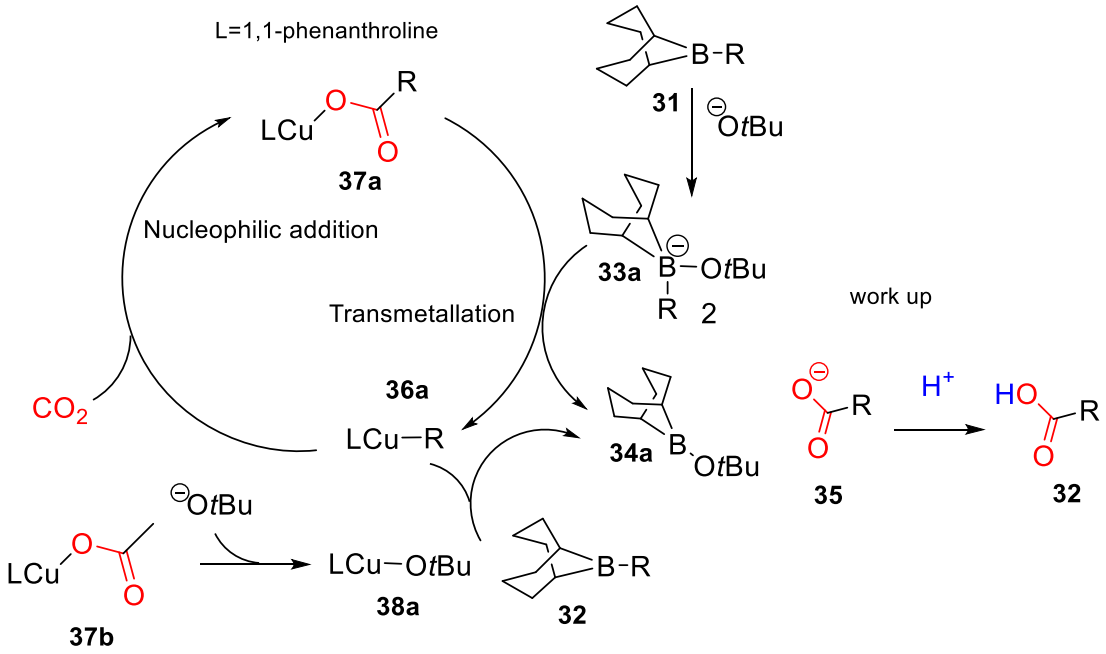
Scheme 15. Cu-catalyzed hydroboration-hydrocarboxylation transformation of terminal olefins.[60,61]

There is however a notably smaller number of carboxylations of alkylboranes, like **31** reported compared to those of aryl- or alkenylboronic esters.[60,61,67,68] The challenge of carboxylizing alkylboranes is in the formation of the transition metal-alkyl species with a

suitable stability and sufficient activity towards CO_2.[62,63] Organoboron compounds can interact with alkoxide bases or hydroxide bases enabling different transition metal-catalyzed cross-coupling reactions. This interaction can be kept as a prerequisite for the carboxylation of alkylboranes.[62,63]

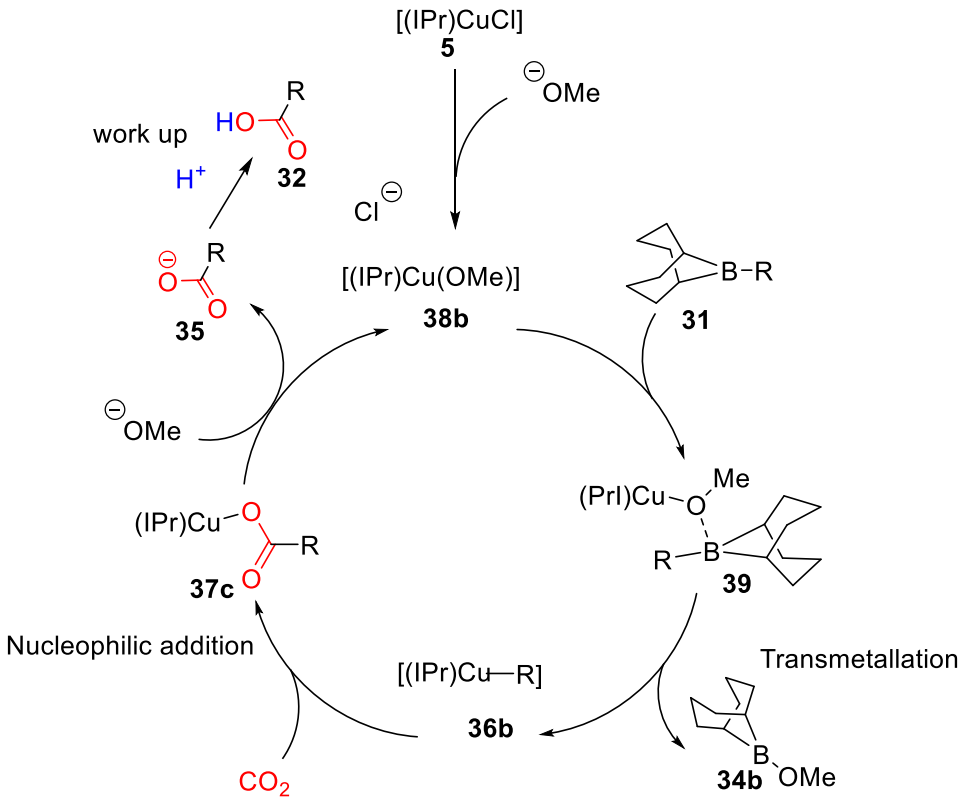
Copper-catalyzed hydroboration-hydrocarboxylation methodology can be used to produce carboxylic acids from terminal olefins.[60,61] Hou and Sawamura have reported a succesful copper catalyzed carboxylation of alkylboranes like **31** with CO_2.[60,61] The monoborylated **31** is readily generated when equimolar amount of diborane reagent **18** reacts with the starting olefin **30** via hydroboration reaction. The subsequnet hydrocarboxylation of **31** produces selectively linear β-carboxylated alkanoic acids **32** (Scheme 15).[60,61] The thorough understanding of the mechanism of this two-step transformation pathway is intriguing in order to apply the approach for far less studied alkynes.

There are two different catalytic pathways predicted for the reaction mechanism. Sawamura *et al* suggested that pathway 1 shown in Scheme 16 would be the predominating mechanism, while Hou *et al* trusted on the pathway 2 shown in Scheme 17. Both catalytic routes presented are possible and neither one can be discarded.[60,61] Especially the choice of the ligand has a direct influence on the mechanism and for that on the catalytic system. Pathway 1 essentially employes a copper catalyst with CuOAc and 1,10-phenantroline ligand, while the pathway 2 uses common NHC-copper catalysts.[60,61]



Scheme 16. Catalytic pathway 1 for synthesis of β-alkanoic acids from terminal olefins.[60,67]

In pathway 1 (Scheme 16) a tetravalent borate adduct **33a** is produced as the result of a stoichiometric reaction of the alkoxide base and the alkylborane reagent **31.**[60,67] The alkyl group from **33a** is transferred to the transition metal center via a subsequent transmetallation, generating an alkylcopper complex [LCuR] **36a.**[60,61,64]A nucleophilic attack of **36a** to CO_2 affords a copper carboxylate intermediate [LCu(OCOR)] **37a.**[60,61,64] The subsequent reaction with **33a** releases an alkoxyboryl compound **34a** and the carboxylate **35** which gives the desired carboxylic acid **32** after aqueous quench. The species **36a** can be alternatively formed as a result of transmetallation between **31** and an alkoxycopper complex **38a** generated from the precatalyst **37b** and the alkoxide base but the mechanistical studies indicate that the formation of the tetravalent borate **33a** rules over the alkoxycopper intermediate **38a.**[60,67]



Scheme 17. Catalytic pathway 2 for synthesis of hydrocarboxylized products from terminal olefins.[61,64]

In comparison to pathway 1**,** the catalytic pathway 2 (Scheme 17) indicates that an instant metathesis reaction of the precatalyst **5** and an alkoxy base generates the catalytically active (IPr)copper alkoxy complex **38b** (see **10** in Scheme 4).[61] In the following step **38b** and alkylborane **31** produce an intermediate **39** in which the oxygen of the alkoxy group interacts with the boryl boron. The transmetallation between copper and boron moieties enables a transfer of the alkyl group to the copper center generating complex **36b,** similarly as in pathway 1. The subsequent nucleophilic addition to CO_2 enables the formation of corresponding **37c**. A σ-bond metathesis between the alkoxy base and **37c** regenerates the catalyst and releases the carboxylate product **35.** The final hydrolysis yields the desired primary carboxylic acid **32**.[36,61,64]

In summary, the strong alkoxide bases are suggested to enhance the σ-bond metathesis reaction of alkylboranes.[60,61] The main difference between the two plausible catalytic routes is related to the reactivity of the alkoxide base and the catalyst system.[60,61] The bulky *t*BuOK came across as a compatible base when used with **37a** and **37b** (Scheme

16). A rapid and complete reaction between **31** and *t*BuOK was approved by Sawamura *et al* with ^{11}B NMR studies elucidating the formation of **33a** and thus suggesting pathway 1. The use of 1,1-phenantroline ligand with CuOAc species turned out to be applicable while NHC-copper catalysts lowered the obtained yields.[61] On the other hand, the less branched MeOLi was more applicable with (IPr)copper species **5** probably due to the relatively longer Cu-O -distance of [IPrCu(OMe)] **38b** in the borate adduct (Scheme 18). For **38b** it was found to be 1.859 Å while for bulkier [IPrCu(O*t*Bu)] the bond length was 1.810 Å.[69] The interaction of the boron from the borate and oxygen from the alkoxy group was confirmed in the x-ray crystallography suggesting the presence of **39** and pathway 2 as the dominating route with NHC-copper-catalystst.[61]

The hydrocarboxylation of alkylboranes is limited to the formation of primary alkanoic acids and the use of strong alkoxide additives is required. Besides this, the carboxylation of secondary alkylboranes does not succeed disclosing the choice of disubstituted olefin substrates.[60,61,64] Another disadvantage of the methodology is a formation of undesired deborated byproducts, which lower the reaction yields especially at raised temperatures.[60]

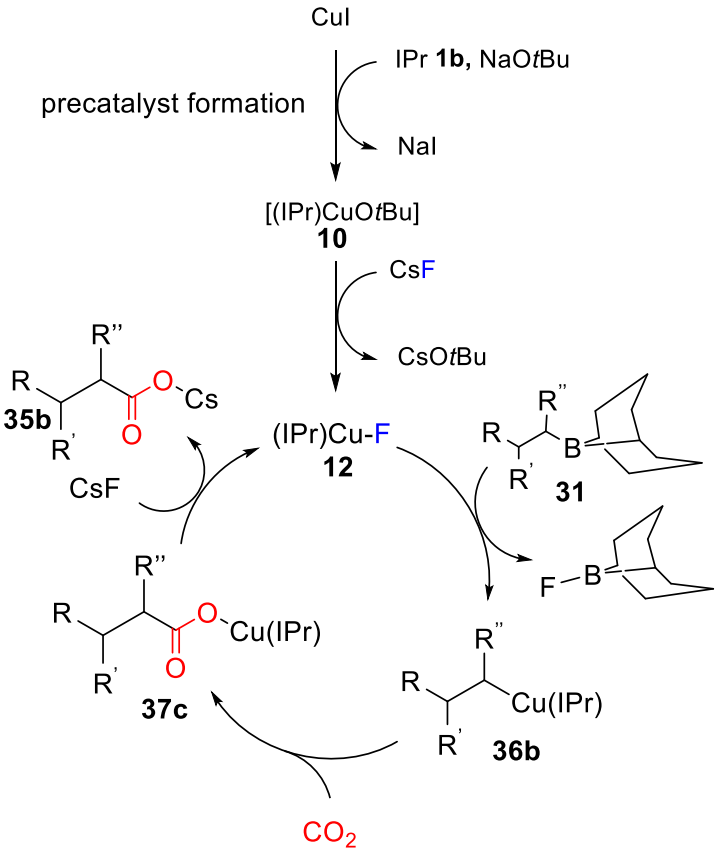
3.3.2 Hydroboration carboxylation of internal olefins and alkynes

The carboxylation of alkylboranes can be extended to include 1,2-disubstituted olefins and terminal alkynes, but a different approach is required for these substrates.[64] The hydroboration with dimer **18** generates corresponding alkyl boranes, similarly as demonstrated in previous section for terminal olefins.[50,64] Terminal alkynes are exposed to produce dihydroborated product analogues of **22** correspondingly in the prevalent conditions**.**[50,64]

According to the study of Skrydstrup *et al* the use of strong alkoxide bases does not initiate the σ-bond metathesis of more sterically demanding disubstituted structures.[64] Milder additives, such as fluoride salts have proved out to be compatible for Miyuara-Suzuki couplings.[65] Based on that information, the use of cesium fluoride was discovered to be crucial for the promotion of the σ-bond metathesis and thus the carboxylation.[64]

Two sequential *in situ* catalyst formations enable the generation of the active NHC-copper fluoride catalyst **12** (Scheme 18). At first, the copper alkoxide precatalyst **10** can be

produced similarly as shown in Scheme 4 but starting from ligand **1b**, copper iodide and sodium *tert*-butoxide.[36,64] Catalyst species **10** can then be treated with CsF in the second step, generating the corresponding fluoride **12** *in situ***.**[64] Species **12** is catalytically very active species but due to a rapid decomposition in solution the *in situ* -generation is preferred.[36] In addition to the rapid hydrid formation between **12** and a hydrosilane described earlier, **12** is inclined to undergo σ-bond metathesis with alkylborane **31** in the same way as shown in Scheme 18.[60,61,64] The transmetallation generates alkylcopper intermediate **36b** which reacts with CO_2 via insertion. The excess of CsF permits regeneration of **12** releasing the carboxylate product **35b** from **37c** respectively. The formation of the fluoride analogue of **39,** in which the fluorine would interact with the boron atom, is still uncertain.[61,64]



Scheme 18. Depicted catalytic cycle for CsF mediated hydroboration-hydrocarboxylation of alkynes.[64]

NHC ligands **1b** and corresponding cyclohexyl analogue **1c** were found to be the most promising ligands for the catalytic system favoring similar pathway as presented by Hou

et al (Scheme 18). [61,64] A copper source is necessary for the reaction initiation, even though CuI itself does not catalyze the carboxylation. In comparison, the reaction did not proceed when phosphonate, phosphine or diamine ligands were employed.[64] Internal unsaturated hydrocarbons, such as cyclohexanes, stilbenes, styrenes and even some natural products can be efficiently carboxylized with this protocol (Figure 7).[64]

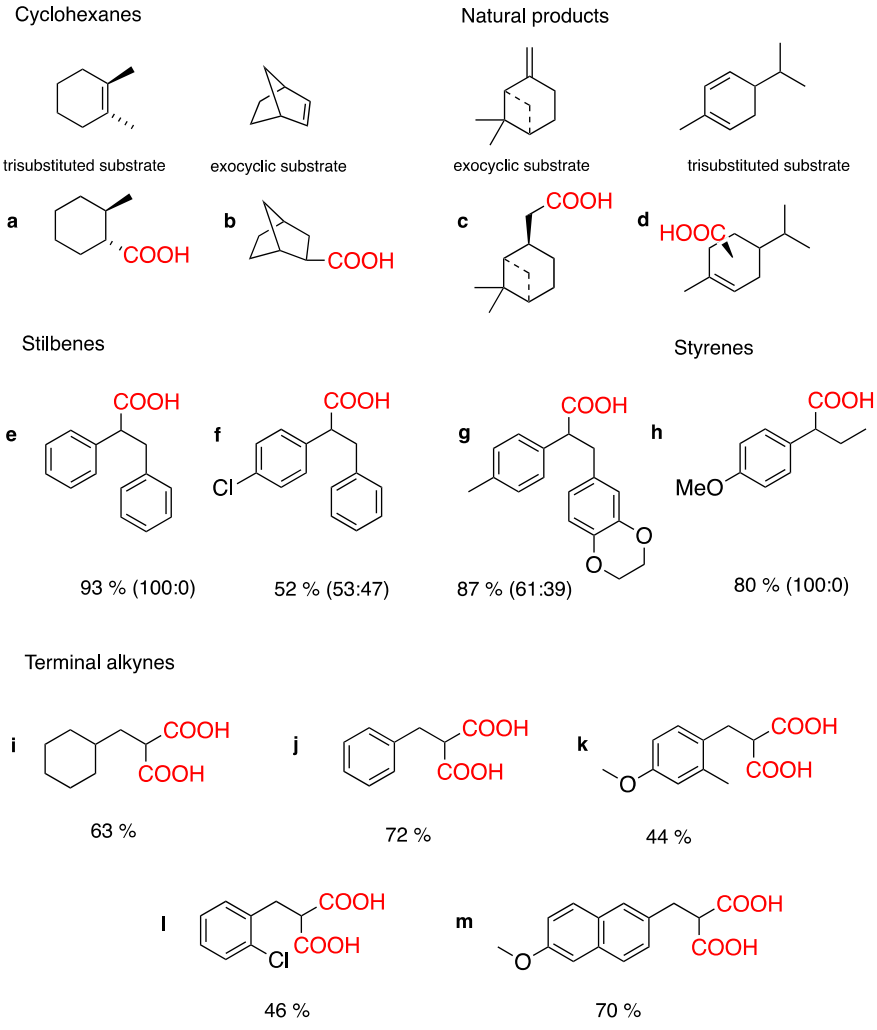


Figure 7. Substrate scope for the two step hydrocarboxylation of internal olefins and terminal alkynes.[64]

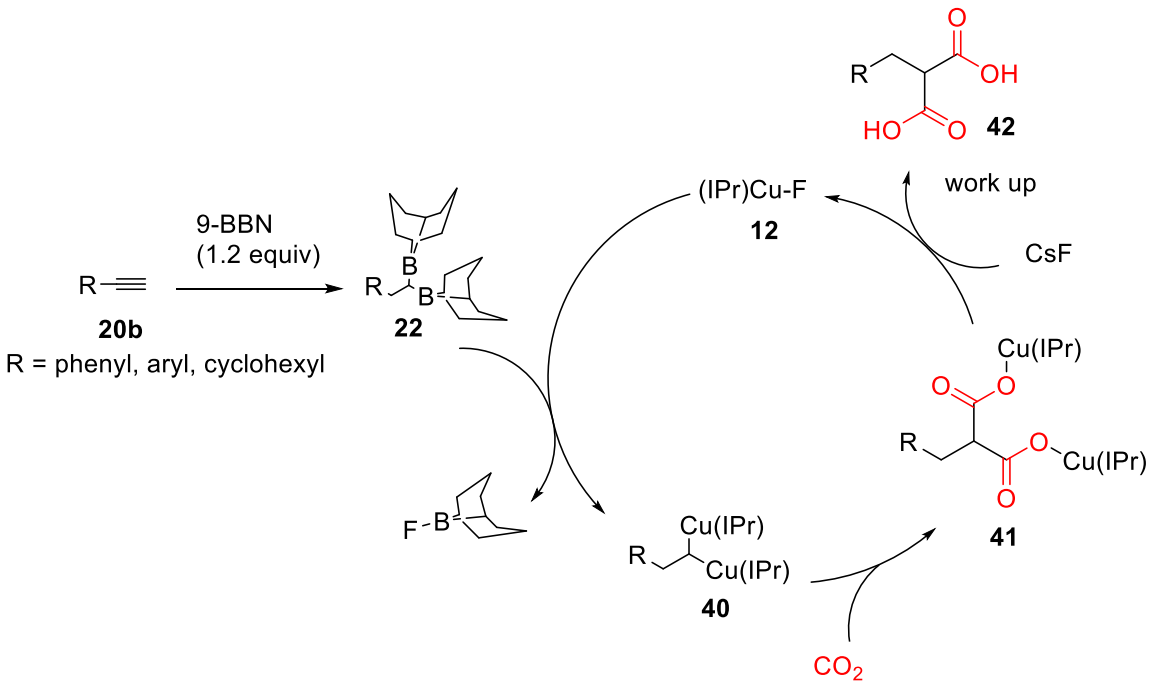
The regioselectivity of the hydrocarboxylation products can be controlled with compatible substituents and their electronic effects. Cyclohexanes **(a-c)** produce single regioisomers depending on the structure of the substrate: exocyclic olefins **(b, c)** produce *exo*-isomers

whereas trisubstituted double bonds produce anti-isomers (**a**) due to the *syn*- addition of the B-H bond.[50,64,57] Substrate (**d)** including two double bonds produces a mixture of both regioisomers with preference towards the less substituted double bond, and the carboxylic group taking place *trans* to the *IPr* group.[64] Stilbenes afford both regioisomers due to the electron rich aryl groups. The selectivity can be modified by tuning the electronic effects of the substituents (**f, g**). Internal styrenes (**h)** produce α-acids as the primary products due to the electron rich aryl substituent on the other side.[60,61,64]

A wide scope of different functionalities can be tolerated in this methodology including pyrroles, indoles, halides and even phosphonic and boronic groups.

Alkynes are known to undergo a double hydroboration with **18** as presented in Scheme 10 earlier in the hydroboration section.[50] Under these prevalent conditions Skrydstrup *et al* introduced the synthesis of malonic acids **42** (**i-m** in Figure 7) via pregeneration of the double hydroborated product analogues of **22** from the starting alkyne **20b** and subsequent carboxylation with CO_2 (Scheme 19). [50,57,64] The *gem*-dibora products can generate a dicopperalkyl-complex **40**, as a result of a double σ-bond metathesis reaction.[50,57,64,66] The CO_2 insertion into **40** will proceed twice respectively, leading to a dicarboxylized intermediate **41**.[64] A mixture of mono- and dicarboxylized products was however obtained by Skrydstrup *et al*, indicating most probably an incomplete double hydroboration step.[50] The formation of considerable amount of monohydroborated species leads to alkanoic acids, like **32**.[61] Correspondingly, the CO_2 insertion may be incomplete resulting in the mixture of the two products.

In common, electron rich terminal aryl alkynes can be transformed smoothly to corresponding diacids, but *ortho*-substituents lower the yields (**l** in Figure 7).



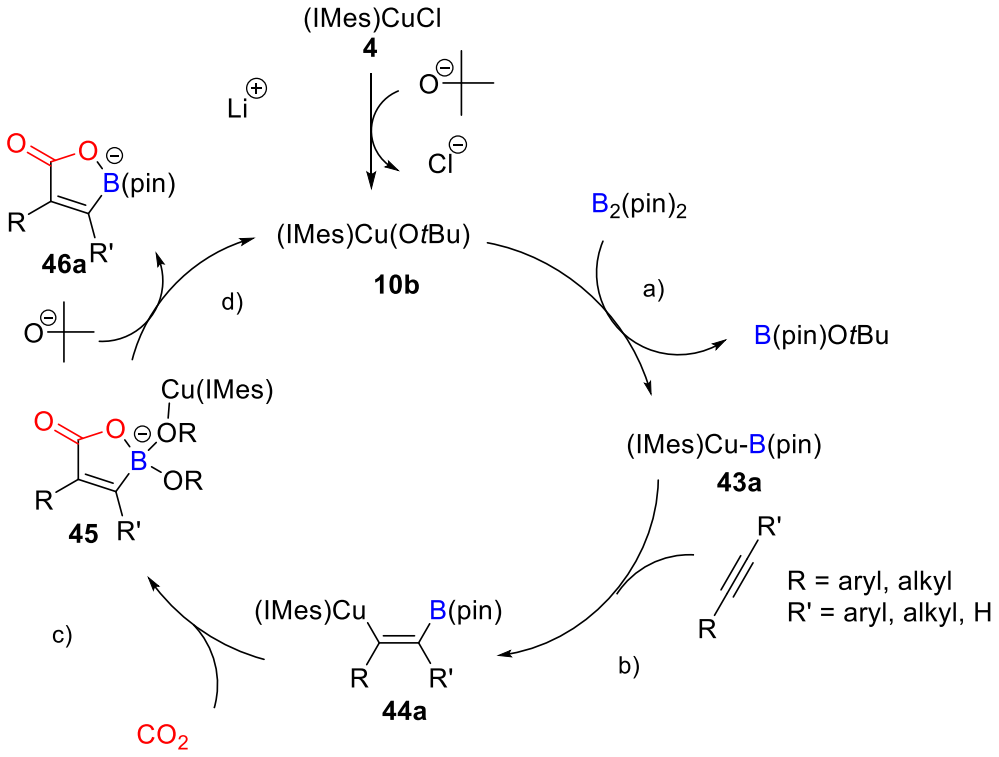
Scheme 19. Plausible catalytic cycle for synthesis of malonic acids from terminal alkynes.[64]

4. Heterocarboxylation of alkynes

The CO_2 based heterocarboxylation of alkynes consists of simultaneous catalytic addition of the carboxylate group and the heteroatom moiety to the triple bond, producing multifunctionalized olefins which are very useful reagents for further synthetic purposes.[71,72] Methodologies for stoichiometric heterocarboxylations have been established within reactive arynes, dienes and allenes using CO_2, but heterocarboxylations of simple unsaturated C-C bonds are less studied.[73,74,75,76] The heterocarboxylation method is useful for the formation of synthetically versatile carbon-boron or carbon-silicon bonds. Nevertheless, the regio- and stereoselective control over the carboxylized products has been generally challenging.[77,78]

N-heterocyclic copper catalysts can be succesfully employed in the boracarboxylation of alkynes, in the presence of diborane reagent **19** and CO_2.[71,72] Zhang *et al* introduced a boracarboxylation methodology, in which both carboxyl group and the boryl moiety are

added regio and stereoselectively affording *β*-boralactones. The reactions proceed via borylcupration and carboxylation steps.[71]

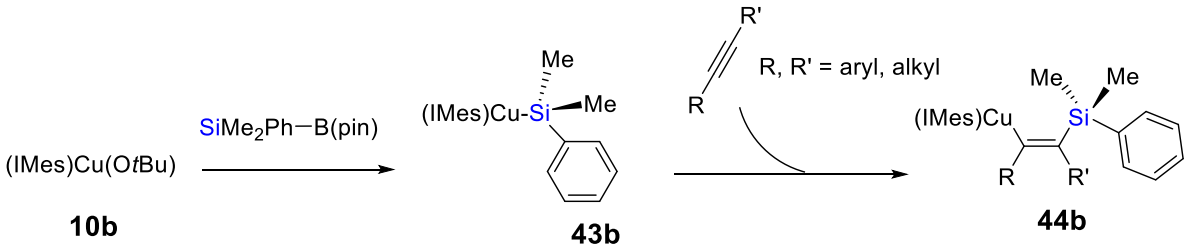


Scheme 20. Boracarboxylation of alkynes. a) boration, b) alkyne insertion, c) carboxylation with CO_2, d) catalyst regeneration.[71]

In the plausible catalytic pathway described in Scheme 21, the reaction proceeds through a nucleophilic attack of the *tert*-butoxide group to the NHC-copper precatalyst **4,** producing a catalytically active copper alkoxide **10b.** This catalyst formation step is similar to the one presented by Hou *et al in* Scheme 18. Complex **10** readily reacts with the diborane **19** via transmetallation forming a [(NHC)Cu-B(pin)] complex **43a**.[70] Subsequent *β*-boryl alkenyl copper complex **44a** is produced via insertion of the alkyne to the C-B bond in *syn*-position (borylcupration). Finally, CO_2 inserts into **44a** generating a hetero carboxylate product **45,** in which the copper moiety is bound to the oxygen atom of the boronic ester. The excess of sodium *tert*-butoxide regenerates the copper catalyst **10b** back to the catalytic cycle releasing a boralactone **46a** as a lithium salt**.**[71,72]

The mechanism indicates that borane dimer **19** readily reacts with **10b** via σ-bond metathesis**,** instead of undergoing hydroboration with the starting alkyne. Correspondingly, the rapid insertion of alkynes into the boryl copper complex **43a** is allowed in high yields at room temperature.[60,70,71] The outpace of hydroboration is probably due to the relatively slow formation of monohydroborated analogue of **24** in the presence of equimolar amount of diborane and internal alkyne, as stated above in hydroboration section (Scheme 10). In comparison, Sawamura, Hou and Skrydstrup utilized a prehydroborated product **(**see **22** and **31)** in the reaction media disclosing the competitive formation of **43a**. Nucleophilic addition of **44a** into CO_2 enables the formation of the heterocyclic product, due to the notable bonding interaction of CO_2 group and the boryl moiety, suggesting that the formation of intermediate **44a** is indispensable in this approach.[70,71]

A comparable silacarboxylation of alkynes can be carried out in the presence of silylboranes and CO_2 with satisfactory regioselectivity.[72] The protocol is nearly identical to boracarboxylation affording silalactones from internal alkynes catalyzed by a copper complexes. The silylborane Me_2PhSi-B(pin) serves as a suitable silicon source reacting immediately with alkoxycopper species **10b**. The resulting silylcopper adduct **43b** is an analogue to the boryl complex **43a,** allowing a significant *syn*-addition to the alkyne. The corresponding β-silyl alkenyl copper species **44b** is disposed to react with CO_2 via nucleophilic addition similarly as complex **44a** presented for boralactones in Scheme 21.[71,72]



Scheme 21. Formation of silylcopper and β-silyl alkenyl copper species in silacarboxylation.[72]

The α,β -unsaturated boralactones can be smoothly synthetized with considerable regioselectivity by employing common NHC-ligands. Disubstituted alkynes with electron rich aryl substituents, such as ethyl esters **a** and thiophene **b** (Figure 8) gave the highest yields. The diphenyl substituted **c** and alkyl substrate bearing **d** were also well tolerated. Terminal alkyne, such as phenyl acetylene produced a quantitative amount of the other stereoisomer, yet giving a considerable yield of **e**. The branched *tert*-butyl substituents **f** did not survive the reaction conditions due to the sterical hindance. The corresponding aryl β-silalactones **g** were obtained entailing also aliphatic functionalities **h.** (Figure 7).[71,72]

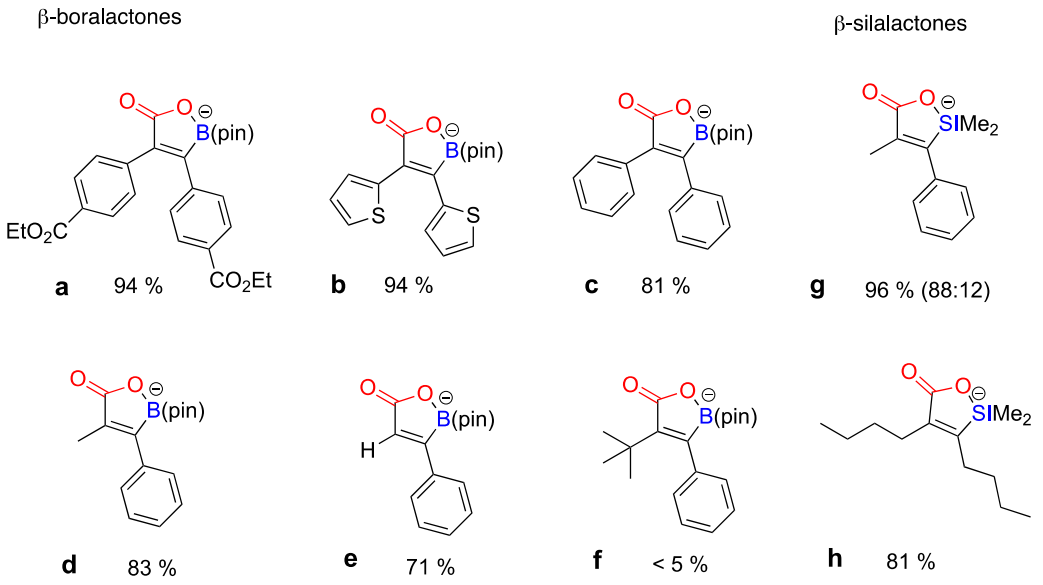
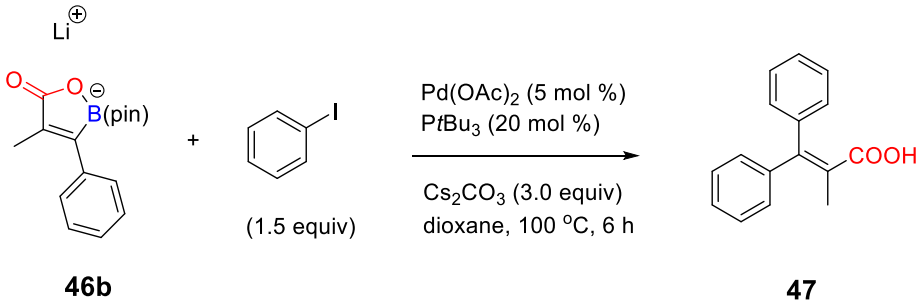


Figure 8. Selected products for bora- and silacarboxylation of alkynes.[71,72]

Interestingly, the ligand choice turned out to be crucial: the less branched IMes **1a** and its saturated analogue SIMes **2a** enabled high yields of the products with a good functional group tolerance, while the more hindered IPr **1b** produced only trace amounts of the products. A similar trend could be observed for the formation of silacarboxylation products in the presence of NHC ligands, indicating that the sterical properties of the NHC ligand would have a strong effect on the conversion of the hetero products. On the other hand, the use of bulky tricyclohexylphosphine and branched tri *tert*-butylphosphine ligands produced β-silalactones in high yields minimizing the formation of the other

regioisomer.[72] In comparison, the phosphine ligand fine-tuning enabled an efficient regiospecific control over the desired regioisomer in silacarboxylation of allenes.[73]

The bora- and silalactones have considerable potential as starting materials for further synthesis of tetrasubstituted olefins.[71] The palladium-catalyzed Miyara-Suzuki cross-coupling reaction cleaves the O-B or O-Si bond due to intramolecular activation of the silicate group or boronic ester group. Electron withdrawing aryl iodides can be used to generate synthetically very useful carboxylic moiety and aryl group bearing olefins, such as **47** (Scheme 23).[71,79,80]



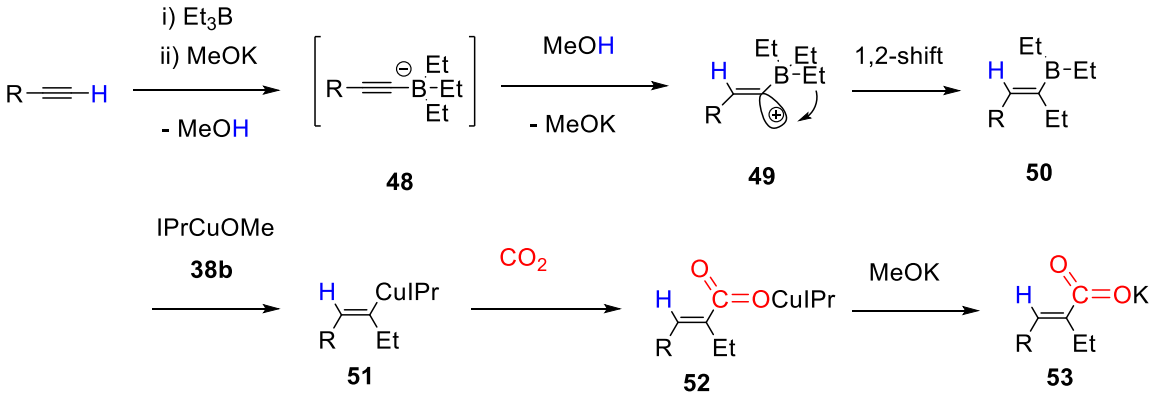
Scheme 22. Miyara-Suzuki coupling reaction of boralactone.

5. Alkylative carboxylation

5.1 Alkylative carboxylation of boronates

The NHC-copper-catalyzed alkylative carboxylation of terminal alkynes produce α-acrylic acids. The reaction mechanism of the alkylative carboxylation is in contrast to the hydrocarboxylation of alkylboranes described in the previous section, due to the employment of strongly electrophilic trialkylboranes, such as Et_3B. The reaction proceeds via a 1,1-carboboration mechanism.[83,84,85] The formation of the acetylide **48** is due to the nucleophilic reaction of alkyne and Et_3B, which is activated by an alkoxy base.[82]

Subsequent protonation of β-carbon produces an intermediate **49**, which then undergoes a 1,2-migration of one ethyl group from the borate boron to the α-carbon position.[81,83] This is due to the donation of electrons from the alkyl group to the empty p-orbital of the carbocation. As a result, an alkylated vinyl intermediate **50** is formed. A copper catalyst **38b** (Scheme 17) is introduced to the boryl adduct **50,** generating the alkenyl copper complex **51** via transmetallation, similarly as presented above in Scheme 18. Subsequent CO_2 insertion produces **52** which releases the acrylic product **53** in the presence of the base.[81]



Scheme 23. Plausable mechanism for alkylative carboxylation of boronates.[81]

This regiospecific methodology produces desired acrylic acids with high E-stereoselectivity shown in Figure 9. The stereocontrol may be related to the protonation of the β-carbon in adduct **49** by the *in situ*-formed MeOH, initiated by the copper catalyst **38b**.[81,84] Noteworthy, only IPr ligand **1b** and its analogues show applicability for this reaction. The choice of the alkoxy base turned out to be crucial as well.[81] Similarly as presented by Sawamura *et al* in Scheme 17, the methoxy base was superior to the bulkier *tert*-butoxide in the activation of alkyne, probably due to the steric effects.[60] The Lewis acidic copper catalyst is presumed to promote the generation of **48** by contributing the acidity of the alkyne.[82] The possible formation of π-alkyne adduct with the copper species is proposed to explain the increased acidity. However, aliphatic alkynes do not produce the corresponding acids in the prevalent conditions probably due to the lower reactivity and insuffucient deprotonation by the base.[81]

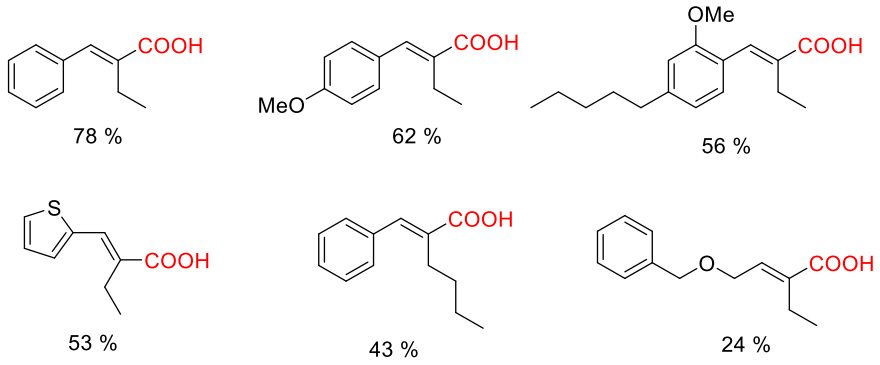
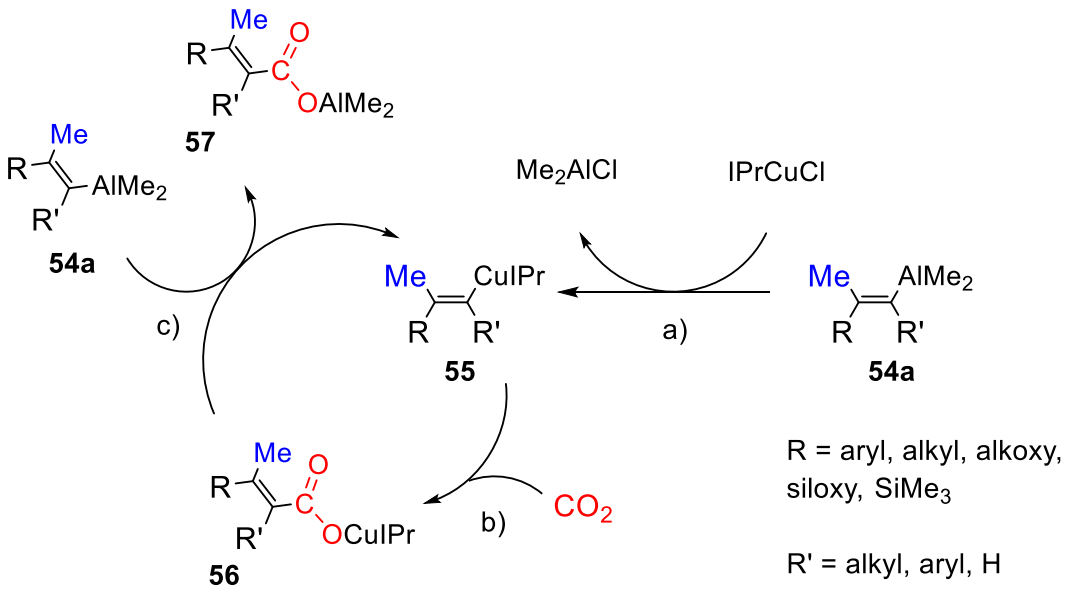


Figure 9. Selected examples of alkylated carboxylic acids.[81]

5.2 Alkylative carboxylation via carboalumination

Various alkynes can be transformed into α,β-unsaturated carboxylic acids alternatively via methylative carboxylation in the presence of reactive aluminum reagents, such as Me_3Al. The procedure consists of two catalytical steps: alkylative alumination of the starting alkyne and subsequent carboxylation.[86,89] The *syn*-addition of Me_3Al species to the alkyne generates a methylated alkenylaluminum complex **54a.**[89] The reaction requires a Ni, Sc or Zr catalyst complex to proceed. Complex **54a** can then undergo carboxylation with CO_2 in the presence of NHC-copper catalyst providing (E)-β-methyl acids in high stereoselectivity, entailing both internal and terminal substrates.[86]

In the plausible catalytic pathway, the complex **54a** is playing a key role due to the two sequential transmetallations between Al and Cu species. At first, the copper alkenyl complex **55** is generated via transmetallation of **54a** and a (IPr)CuCl species. The CO_2 insertion produces adduct **56** which is exposed to undergo further transmetallation with **54a** releasing the aluminum carboxylate product **57**.[86,88]

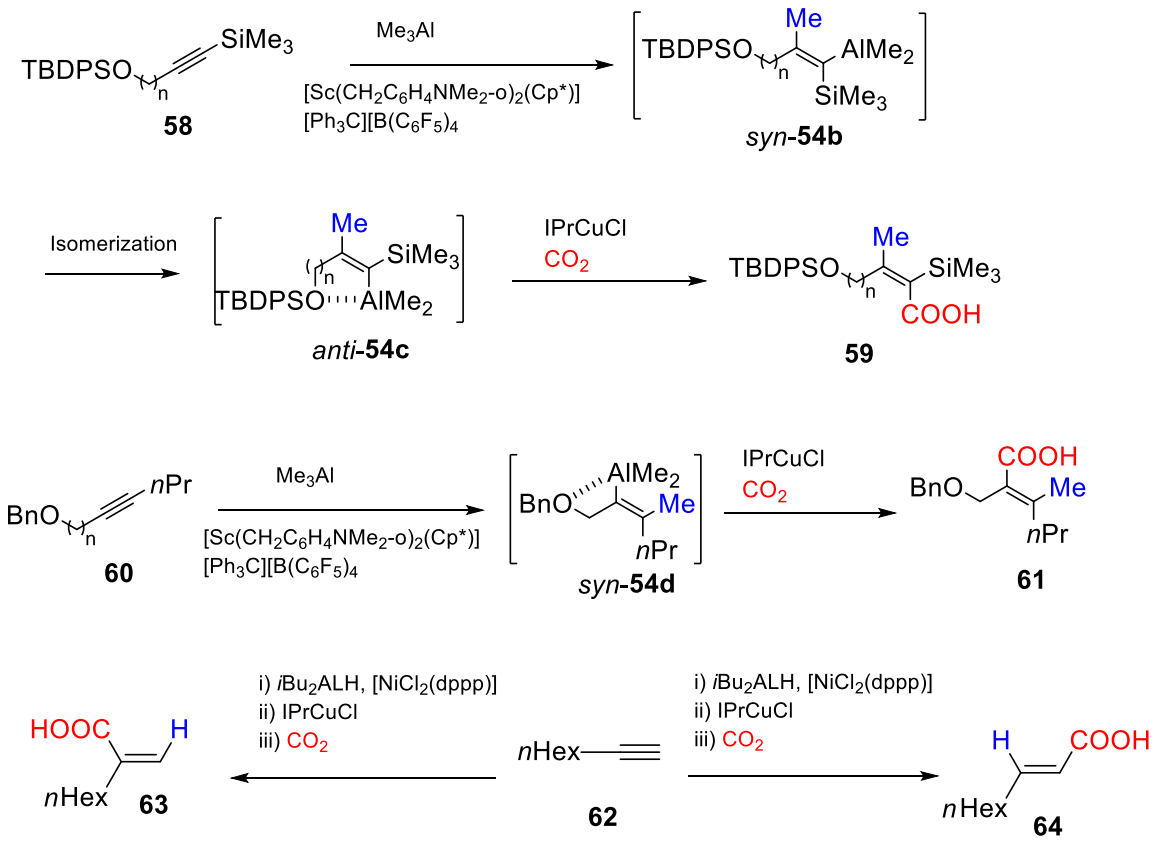


Scheme 24. Plausable mechanism for alkylative carboxylation of alkynes via carboalumination. a) transmetallation, b) CO_2 insertion, c) second transmetallation.[86]

The alumination step shows both regio- and stereospecifity due to the strong electronic effects of the alkyne substituents. The catalyst system can also be fine-tuned to achieve high selectivity. The aluminum moiety can be added at both α- and β-carbon positions of the triple bond. Subsequently, the carboxylic group will adopt the same position providing the desired regio product.

For instance, trimethylsilane-bearing alkyne **58** favors the formation of an *anti*-isomer **54c** due to the isomerization of the *syn*-adduct **54b**.[86] As a result, an *anti*-product **59** is obtained. The TMS moiety has a directing effect of the aluminum unit to the distal position from the ether substituent like in **54b** while BnO and siloxy groups direct the alumination to occur at the proximal position producing intermediate with another regiochemistry, such as **54d** and the corresponding carboxylic acid **61**.[87,89] The tethered-oxygen may also affect the regioselectivity via chelation interactions, seen in **54c** and **54d**.

In addition, the protocol can be extended to hydrogenative carboxylation of terminal alkynes by replacing Me_3Al reactant with aluminum hydride reagent, such as iBu$_2$AlH. The choice of Ni-catalyst used for the hydrogenative alumination step predetermines the resulting regioisomer. Both carboxylic acids **63** and **64** can be generated regioselectively from alkyne **62** by tuning the ligand of the catalyst.[86]



Scheme 25. Effect of the alkyl substituents and catalyst system to the regio- and stereoselectivity of carbalumination.[86]

II. Experimental

1. Introduction

The goal of this research was to detect various carboxylation pathways for alkynes with NHC-copper catalysts and CO_2. The NHC-copper hydrid-based catalyst is known to efficiently transform alkynes to corresponding carboxylic acids, but the pathway mostly entails electron rich internal alkynes. In contrast, a hydroboration-based two step carboxylation is well known for olefins, but it has been only applied for/on a handful of terminal alkynes. Therefore, it was intriguing to broaden the substrate scope for these known methodogies and fine-tune the copper catalyst system. Finally, a heterocarboxylation pathway was explored with the NHC-catalysts.

The experimental part consists of the synthesis of the NHC ligands and their corresponding NHC-copper catalysts. Further on, NHC-copper hydride-catalyzed hydrocarboxylation of alkynes, tandem hydroboration-carboxylation of alkynes and boracarboxylation of alkynes will be presented.

2. General

Unless otherwise stated, all manipulations were carried out under an inert argon atmosphere using standard Schlenk-type glasswares and Schlenk techniques on a (dual bank manifold) Schlenk line system and in a Mbraun Unilab argon-filled glovebox. Anhydrous solvents THF, hexane, toluene and DCM were obtained from the solvent dryer (Vac solvent purification system) and degassed by freeze-pump-thaw cycling before the use. 1,4-dioxane, benzene and pentane were distilled and then degassed respectively. The solvents were stored over activated 3Å molecular sieves. All the other solvents used were

HPLC quality. CCl_4, anilines and phenylacetylene were obtained from Sigma-Aldrich and they were distilled prior to use. The hydrosilanes and organoboranes were obtained from Sigma-Aldrich and they were restored in glovebox. All the other substances were purchased from Sigma-Aldrich, Alfa Aesar, TCI and ACROS and they were used. without further purification unless otherwise mentioned.

3. Analysis methods

NMR solvents CD_2Cl_2, C_6D_6, DMSO and MeOD, were used as received. The NMR data for ^1H, ^{13}C, ^{11}B and 19F NMR spectra were recorded on a Bruker 400 and 500 MHz spectrometers. The chemical shifts are expressed in ppm (parts per million) and referred to signal of TMS (0.00 ppm) and $CDCl_3$ (77.0 ppm) in ^1H and ^{13}C spectra, respectively. For NMR spectra Following abbreviations were used for signal multiplicities: s-singlet, d-doublet, t-triplet, q-quartet, quin-quintet, m-multiplet, b-broad. Coupling J-constants are mentioned in Hertz (Hz).

GC analysis was carried out using an Agilent Technologies 6890N GC equipped with 5973 MSD, using an Agilent HP-Ms-5-UI (30 m, 0.25 mm, 0.25 µm) column.

The column chromatography was performed using 40-63 µm particle size silica gel.

4. Synthesis of NHC ligands

4.1. Glyoxal-bis-(2,4,6-trimethylphenyl) imine

A 250 mL round bottom flask equipped with a magnetic stirrer was loaded with 10 mL of 2,4,6-trimethylaniline (71.2 mmol, 2 equiv) and 4 mL (35.0 mmol, 1 equiv) of 40 w% glyoxal in water and EtOH as a solvent (50 mL). 1,0 mL (0.035 equiv) of formic acid was added as a catalyst with vigorous stirring. A yellow precipitate was formed after addition and the solution was additionally stirred for 1 hour at rt. The solid was filtrated and washed first with 100 mL of ice cold EtOH and then 100 mL of ice cold Et_2O.

The product was dried under vacuum overnight to give yellow solid powder **1**. (11.3 g, 55%)

^{1}H NMR ($CDCl_3$, ppm) δ 2.20 (s, 12H, *ortho*-CH_3), 2.33 (s, 6H, *para*-CH_3), 6.95 (s, 4H, CH phenyl), δ 8.14 (s, 2H, HC=N).

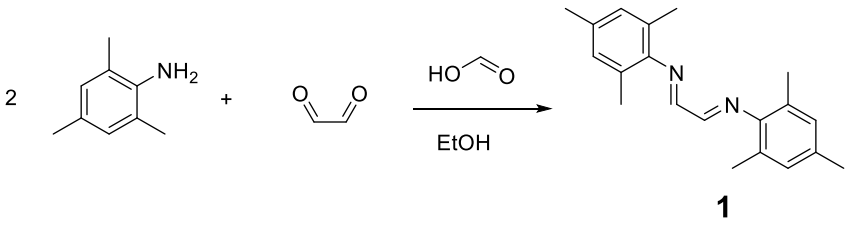


Figure E1: Synthesis of compound **1.**

4.2. 1,3-bis(2,4,6-trimethylphenyl)-imidazolium chloride, IMesHCl

A 3-neck flask equipped with a magnetic stirrer, dropping funnel and reflux condenser was loaded with 3,9g of **1** (13,0 mmol) in 100 mL of EtOAc. The solution was heated to reflux slowly and 0,41 g (13,7 mmol, 1,03 equiv) of paraformaldehyde was added at once and flushed with 5 mL of EtOAc. The reaction mixture was kept under reflux for 15 minutes and subsequently 1,7 mL (13,0 mmol, 1,03 equiv) of TMSCl in 20 mL of EtOAc was slowly added during 15 minutes via a dropping funnel vigorously stirring. The addition time is crucial for the reaction to succeed. Light brown solid formation was observed after the addition was completed. The refluxing was continued for 3 more hours in 70 °C. After that, the reaction mixture was cooled to rt. Further on it was kept in the freezer overnight. Then the crude product was washed with 150 mL of ice cold EtOAc. Finally, the light brown solid product **2** was dried under vacuum overnight (3.78 g, 86%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 2.23 (s, 12 H, *ortho*-CH_3), 2.37 (s, 6 H, *para*-CH_3), 7.06 (s, 4 H, CH phenyl), 7.58 (s, 2 H, CH_2=CH_2), 11.11 (s, 1H, N=CH-N) (See Figure E7).

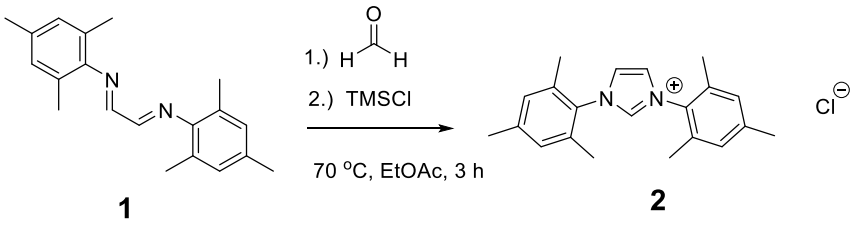


Figure E2: Synthesis of compound **2.**

4.3. Glyoxal-bis(2,6-diisopropylphenyl) imine

A 250 mL round bottom flask equipped with a magnetic stirrer was loaded with 9,1 mL of 2,6-diisopropylaniline (71,2 mmol, 2 equiv) and 4 mL (35,0 mmol, 1 equiv) of 40 w% glyoxal in water and EtOH as a solvent (50 mL). 1 mL (0,035 equiv) of formic acid was added as a catalyst with vigorous stirring. Exceed of glyoxal solution addition should be avoided due to the hard solid formation. The reaction mixture was heated to 50 °C for 15 minutes and then cooled down to rt. Yellow precipitate was formed after the cooling and the solution was then stirred for 5 hours at rt. The solid was filtrated and washed first with 100 mL of ice cold EtOH and then 100 mL of ice cold Et_2O.

The product was then kept under vacuum overnight to give a yellow solid powder **3**. (9,20 g, 34%)

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.23 (d, $^3J_{H\text{-}H}$ = 6.8 Hz, 24 H, *IPr*-CH_3), 3.00-2.93 (m, 4 H, *IPr*-H), 7.23-7.16 (m, 6 H, CH_3 phenyl), 8.12 (s, 2H, H-C=N).

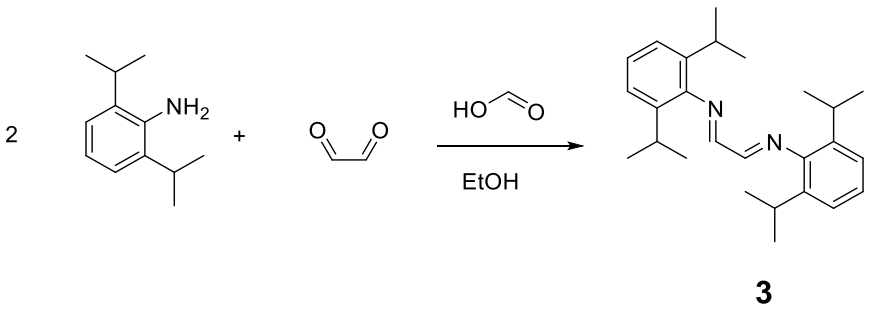


Figure E3: Synthesis of compound **3.**

4.4 1,3-bis(2,6-diisopropylphenyl)-imidazolium chloride, IPrHCl

A 3-neck flask equipped with a magnetic stirrer, dropping funnel and reflux part was loaded with 4,9 g of **3** (13,0 mmol, 1,0 equiv) in 100 mL of EtOAc. The solution was heated to reflux slowly and 0,41 g (13,7 mmol, 1,03 equiv) of paraformaldehyde was added at once and flushed with 5 mL of EtOAc. The reaction mixture was kept under reflux for 15 minutes and subsequently 1,7 mL (13,0 mmol, 1,03 equiv) of TMSCl in 6 mL of EtOAc was slowly added during a period of 35 minutes via a dropping funnel vigorously stirring. Light brown solid formation was observed after the addition was completed. The reaction mixture was additionally refluxed for 3 hours at 70 °C. After that, the reaction mixture was cooled to rt and kept in the freezer overnight. Then the crude product was washed with 150 mL of ice cold EtOAc. Finally, the light brown solid **4** product was dried under vacuum for couple of hours. (2.92 g, 62 %)

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.25 (d, $^{3}J_{H\text{-}H}$ = 6.7 Hz, 12 H, CH-CH_3), 1.32 (d, $^{3}J_{H\text{-}H}$ = 6.7 Hz, 12 H, CH-CH_3), 2.48 (m, 4 H, CH-CH_3), 7.39 (d, $^{3}J_{H\text{-}H}$ = 7.7 Hz, 4H, CH phenyl), 7.60 (t, $^{3}J_{H\text{-}H}$ = 7.7 Hz 2 H, CH phenyl), 8.09 (s, 2 H, CH_2=CH_2), 9.70 (s, 1H, N=CH-N) (See Figure E8).

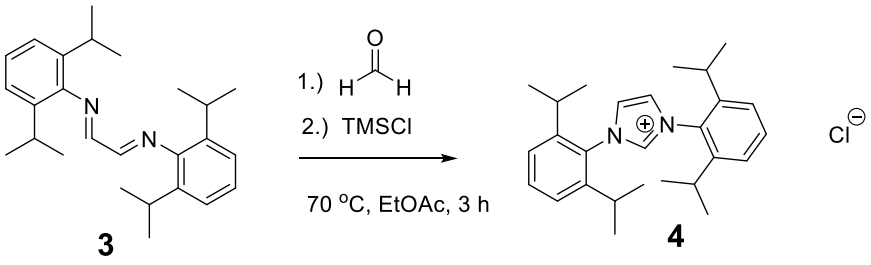


Figure E4: Synthesis of compound **4.**

5. Synthesis of imidazolium copper(I)chlorides

5.1. 1,3-bis(2,4,6-trimethylphenyl)-imidazolium copper(I) chloride, Cu(IMes)Cl

Procedure A

In theglovebox, to a 25 mL Schlenk vessel equipped with a magnetic stirrer was weighted 800 mg of **2** (2.34 mmol) and 220 mg of Cu_2O (1.55 mmol, 0.67 equivalents). Around 4-5 mL of DCM was added to the vessel and it was stirred at rt for 48 hours. The crude reddish product was dissolved in 3 mL of fresh DCM and filtrated over a silica bed in a 30 mL glass fritted funnel using a vacuum filtration. The filtrate was taken out of the glovebox and the solvent was evaporated under vacuum. The solid was washed (under Ar) with degassed water and dried under vacuum giving an off-white powder as a product **5** (545 mg, 58%).

Procedure B

In the glovebox, to a 25 mL Schlenk vessel equipped with a magnetic stirrer was weighted cuprous 220 mg chloride (2.20 mmol, 1.0 equiv), 800 mg of **2** (2.34 mmol, 1.05 equiv) and 607 g of potassium carbonate (4.40 mmol, 2.00 equiv). 7.5 mL of 3-chloropyridine was added as a solvent. The reaction mixture was taken out of the glovebox and stirred 16 hours in 110 °C. After cooling to rt the reaction mixture was taken back to glovebox and a minimun amount of DCM (10 mL) was added to dissolve the product. The crude brownish product was vacuum filtrated through a short silica bed with a short plug of celite on top of it and the solvent was then evaporated under vacuum. The residual was treated with pentane and then kept under vacuum to give off-white powder (330 mg, 35%).

Procedure C

Under air, to a 25 mL Schlenk vessel equipped with a magnetic stirrer was weighted 150 g of NHC ligand **2** (0.44 mmol, 1 equiv) and 145 mg of copper powder (s) (2.30 mmol, 5 equiv) in 5 mL of MeCN. The reaction mixture was stirred at 55 °C for 26 hours. After cooled down to rt 3 mL of fresh MeCN was added to dissolve the product with a simultaneous gentle warming (30-40 °C). Subsequently the recrystallization of the crude product with addition of cold Et_2O (7 mL) and MeCN (10 mL), was performed. The

Schlenk was taken to the freezer overnight and filtrated under vacuum. Only trace amounts of the desired product **5** was obtained.

^{1}H NMR (400 MHz, $CDCl_3$): δ 2.11 (s, 12 H, CH_3), 2.34 (s, 6 H, CH_3), 7.00 (s, 4 H, CH phenyl), 7.05 (s, 2 H, CH_2=CH_2) (See Figure E9).

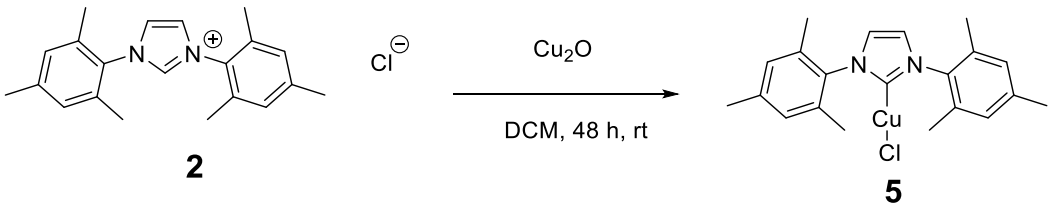


Figure E5: Synthesis of compound **5.**

5.2. 1,3-bis(2,6-diisopropyl)-imidazolium copper(I) chloride, Cu(IPr)Cl

In the glovebox, to a 25 mL Schlenk vessel equipped with a magnetic stirrer was weighted 990 mg of **4** (2.34 mmol) and 220 mg of Cu_2O (1.56 mmol, 0.67 equivalents). Around 4-5 mL of DCM was added to the vessel and it was stirred at rt for 48 hours. The crude product was dissolved in 3 mL of fresh DCM and filtrated over a silica bed in a 30 mL glass fritted funnel using a vacuum filtration. The filtrate was taken out of the glovebox and the solvent was evaporated under vacuum. The solid was washed (under Ar) with degassed water and dried under vacuum giving an off-white powder as a product **6** (742 mg, 65%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.24 (d, $^3J_{H-H}$ = 6.9 Hz, 12 H, CH-CH_3), 1.31 (d, $^3J_{H-H}$ = 6.9 Hz, 12 H, CH-CH_3), 2.58 (m, $^3J_{H-H}$ = 6,9 Hz, 4 H, CH-CH_3), 7.13 (s, 2 H, CH_2=CH_2), 7.31 (d, $^3J_{H-H}$ = 7.8 Hz 4 H, CH phenyl), 7.49 (m, $^3J_{H-H}$ = 7.8 Hz, 2 H, CH phenyl) (See Figure E10).

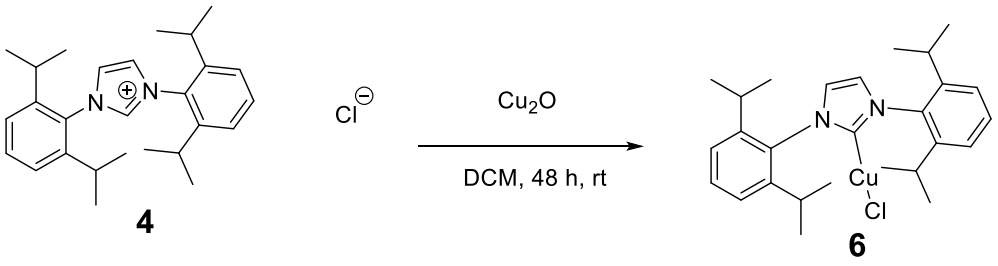


Figure E6: Synthesis of compound **6.**

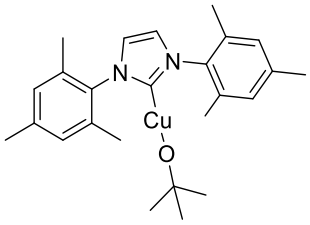
Table 1. Screening of reaction conditions

Entry	Cu source	Equiv of Cu	Solvent	Base	T (°C)	t (h)	Yield (%)
1	Cu_2O	0,85	DCM		rt	48	32
2	Cu_2O	0,67	DCM		rt	24	58
3	Cu_2O	0,85	Toluene		100	24	39
4	Cu_2O	0,67	H_2O		100	24	60
5	CuCl	1,05	pyridine	K_2CO_3	110	16	trace
6	CuCl	1,05	3-chloropyridine	Na_2CO_3	110	16	29
7	CuCl	1,05	3-chloropyridine	K_2CO_3	110	16	35
8	Cu powder	1,0	MeCN		55	26	trace[a)]

a) Performed underair

6. Synthesis of NHC-Copper-*tert*-butoxides and fluorides

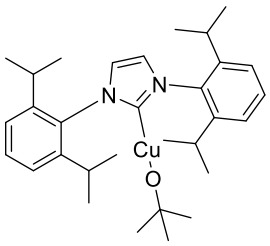
6.1. [1,3-Bis(2,4,6-trimethyl) imidazol-2-ylidene]copper(I) tert-butoxide, [IMesCuO*t*Bu]



7

In the glovebox, to a 25-mL Schlenk vessel equipped with a magnetic stirrer was added 600 mg of [IMesCuCl] **5** (1.50 mmol) and 145 mg of sodium *tert*-butoxide (1.50 mmol) in THF (6.0 mL). The resulting brown solution was stirred for 6 h at rt in glovebox and the mixture was filtered through a celite bed under vacuum. The Schlenk was then taken out of the glovebox and concentrated under vacuum affording a tan powder, 250 mg. The product could not be purified, or it decomposed hence the yield was not determined and NMR data is not reported (See Figure E11).

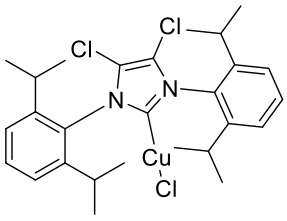
6.2. [1,3-Bis(2,6-diisopropylphenyl) imidazol-2-ylidene]copper(I) tert-butoxide, [IPrCuO*t*Bu]



8

In the glovebox, to a 25-mL Schlenk vessel equipped with a magnetic stirrer was added 730 mg of [IPrCuCl] **6** (1.50 mmol) and 145 mg of sodium *tert*-butoxide (1.50 mmol) in THF (6.0 mL). The resulting brown solution was stirred for 6 h at rt in the glovebox and the mixture was filtered through a celite bed under vacuum. The Schlenk was then taken out of the glovebox and concentrated under vacuum affording a tan powder, 540 mg. The product could not be purified completely, or it decomposed hence the yield was not determined. Absence of *tert*-butoxy signals in ^{1}H NMR studies indicates decomposition of the product hence NMR data is not reported (See Figure E12). The product was used directly as a substrate for the synthesis of **11.**

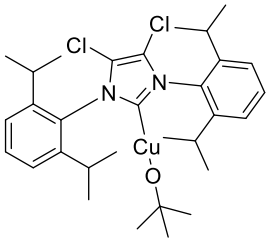
6.3 [4,5-dichloro-1,3-bis(2,6-diisopropylphenyl imidazol-2-ylidene]copper(I) chloride, [Cl_2IPrCuCl]



9

In the glovebox, to a 25-mL Schlenk vessel equipped with a magnetic stirrer was added 640 mg of IPr ligand **4** (1.50 mmol, 1 equiv) and 210 mg of potassium *tert*-butoxide (1.60 mmol, 1.05 equiv) in THF (6.0 mL). The resulting brown solution was stirred for 1 h at rt in glovebox and the mixture was filtered through a celite bed under vacuum to remove potassium chloride salts. 0.30 mL of CCl_4 (3.10 mmol, 2.1 equiv) was added to the reaction mixture and the stirring was continued for 5 hours. Then 0.33 g of CuCl was added and the stirring was continued an additional 5 hours. The suspension was taken out of the glovebox and concentrated in vacuo. The attempts for purification of the crude product with column chromatography using EtOAc and then DCM as eluents failed.

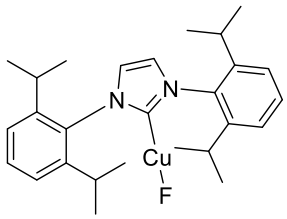
6.4. [4,5-dichloro-1,3-bis(2,6-diisopropylphenylimidazol-2-ylidene]copper(I)tert-butoxide, [Cl_2IPrCuO*t*Bu]



10

In the glovebox, to a 25-mL Schlenk vessel equipped with a magnetic stirrer was added 730 mg of [IPrCuCl] complex **6** (1.50 mmol, 1 equiv) and 155 mg of sodium *tert*-butoxide (1.60 mmol, 1.05 equiv) in THF (6.0 mL). The resulting brown solution was stirred for 6 h at rt in glovebox and the mixture was filtered through a celite bed under vacuum. Then, 0.30 mL of CCl_4 (3.10 mmol, 2.1 equiv) was added to the reaction mixture and the stirring was continued for 5 hours. The suspension was taken out of the glovebox and concentrated in vacuo. The attempts for purification of the crude product with column chromatography using EtOAc and then DCM as eluents failed.

6.5. [1,3-bis(2,6-diisopropylphenylimidazol-2-ylidene]copper(I) fluoride, [IPrCuF]



11

In the glovebox, to a 25-mL Schlenk vessel equipped with a magnetic stirrer was added 480 mg (0.80 mmol, 1 equiv) of [*IPr*CuO*t*Bu] **8** (0.80 mmol) and benzene (8.0 mL). 45 µL of (0.26 mmol, 0.33 equiv) triethylamine tris(hydrofluoride) was added as a fluorinating agent to the solution. The mixture was stirred for 6 hours and concentrated in vacuo. The residue was taken back to the glovebox and suspended with 4 mL of pentane. The obtaned white slurry was filtrated under vacuum and washed with 8 mL of pentane to give white solid (150 mg, 34%). The product could not be purified completely. This is probably due to the decomposition or unstability in the benzene solution. Absence of corresponding fluorine signals in ^{19}F NMR studies indicate the decomposition of the compound (See Figure E13).

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.25 (s, 12 H, CH-CH_3), 1.33 (s, 12 H, CH-CH_3), 2.58 (broad, 4 H, CH-CH_3), 7.17 (s, 2 H, CH_2=CH_2), 7.32 (d, $^{3}J_{H-H}$ = 7,2 Hz 4 H, CH phenyl), 7.52 (broad, 2 H, CH phenyl).

7. Synthesis of carboxylic acids with NHC-copper catalyst via hydroboration-hydrocarboxylation method

7.1. Terminal alkynes - Carboxylation procedure 1

Hydroboration step

To a 25 mL Schlenk tube equipped with a magnetic stirrer was weighted 80 mg of *H*-9-BBN-dimer (0.33 mmol, 1.1 equiv) and it was dissolved to 1.5 mL of 1,4-dioxane. Then 0.30 mmol (1 equiv) of terminal alkyne was added via syringe. The mixture was sealed with a rubber septum, taken out of the glovebox and set to a pre-heated oil bath at 65 °C. The reaction was allowed to stir for 18 hours forming a clear yellow solution.

Hydrocarboxylation step

After the hydroboration was complete the reaction mixture was cooled down to rt and taken back to the glovebox. To another 25 mL Schlenk tube equipped with a magnetic stirrer was weighted 15.3 mg (0.036 mmol, 12 mol %) of IPr ligand. 3.45 mg (0.036 mmol, 12 mol %) of sodium *tert*-butoxide was subsequently added together with 5.7 mg of CuI (0.030 mmol, 10 mol %). The resulting mixture was dissolved in 0.75 mL of dioxane and stirred in the glovebox for 1 hour. 100 mg (0.67 mmol, 2.2 equiv) of CsF in 0.75 mL of dioxane was stirred in a vial in the glovebox simultaneously for 1 hour. Both solutions were then added together to the initial schlenk tube containing the hydroboration product. The schlenk tube was resealed with a rubber septum and taken out of the glovebox. The tube was kept under vacuum for a short while. Then a balloon filled with CO_2 was stabbed through the septum via a syringe engendering a carbon dioxide atmosphere. The reaction mixture was stirred for 18 hours in 100 °C.

Work up

The schlenk tube was cooled down and the solution was transferred to a separation funnel together with 10 mL of Et_2O and 10 mL of saturated aqueous sodium bicarbonate solution, $NaHCO_3$ (aq). An extraction with $NaHCO_3$ was repeated three times in order to trap the ionic carboxylate product to the aqueous phase. The combined aqueous portions were first washed with 5 mL of Et_2O and then treated with 6 M HCl in a beaker until the solution turned acidic. The aqueous solution was returned to the extraction funnel and extracted three times with 10 mL of Et_2O. The organic phases were collected and dried over Na_sSO_4. After filtration the solvent was removed in a rotary evaporator and the product was then dried under vacuum. The primary carboxylic acids were obtained after purification of crude products by flash column chromatography. 20:1 DCM/MeOH was used as an eluent. The products were obtained as off-white solids.

7.2. Internal alkynes – Carboxylation procedure 2

The hydroboration-hydrocarboxylation of internal alkynes followed the same synthetical route as the one presented for terminal alkynes in procedure 1. 0.4 mmol (1 equiv) of the substrate and 107 mg (0.44 mmol, 1.1 equiv) of *H*-9-BBN-dimer were used for the hydroboration step. Other reactants were scaled up correspondingly: 20.4 mg (12 mol %) of IPr ligand, 4.6 mg (12 mol %) of Na*t*BuO and 7.6 mg (10 mol %) of CuI for the pre catalyst formation. 133 mg (2.2 equivalents) of CsF for the *in-situ* IPrCuF- catalyst formation.

The bulkier disubstituted products precipitated during the work up step due to the acidic quench. This might be due to the poorer solubility to the aqueous phase.

The 1,2-disubstituted carboxylic acids were obtained after purification of crude products by flash column chromatography. 5:1 Hexane/EtOAc was used as an eluent. The products were obtained as off-white solids.

7.3. Sample preparation for GC analysis

After work up, the crude product was dissolved in EtOAc and diluted in a 50 mL volumetric flask. Acetophenone (40 µL) was then added as an internal standard.

GC samples were prepared by passing 1.5 mL of the solution through a short silica plug (1 cm thick). The yields were determined by using GC-MS with calibration curves.

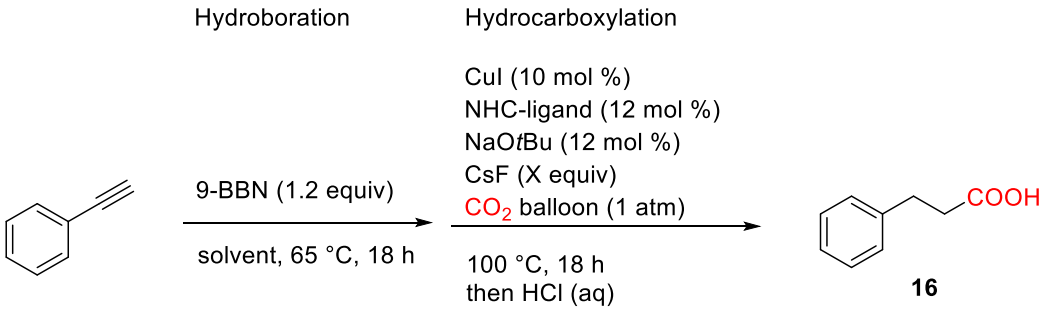
7.4. Optimization of the reaction conditions and product scope

The optimization study of the reaction conditions for the tandem hydroboration-carboxylation pathway was performed employing simple terminal alkyne, phenyl acetylene with 1.2 equivalents of 9-BBN dimer for the initial hydroboration step. The (NHC)Cu*t*BuO precatalyst was prepared from CuI, NHC ligand and sodium *tert*-butoxide separately in a solution of 1,4-dioxane. CsF was further added to this solution affording

the (NHC)CuF. The final carboxylation was performed under CO_2 balloon. The yields of the products were obtained with the GC-Ms. Both IMes (**2**) and IPr (**4**) ligands provided the hydrocinnamic acid **16** in considerable yields of 23 % and 25 % in 1,4-dioxane (table 2, entries 1 and 6). In addition, employing the IPrCuCl (**6**) complex with increased amount of CsF (3.0 equiv) present, afforded a comparable isolated yield of 22% (table 2, entry 2). The replacement of 1,4-dioxane with THF or hexane afforded **16** only in trace amounts (table 2, entries 3 and 4). The reaction did not proceed in the absence of CsF or alkoxy base (table 2, entries 7 and 8).

The reaction of internal diphenyl acetylene afforded (E)-2,3-diphenyl acrylic acid **12** in 45 % yield (table 3, product **12**). Another internal aryl alkyne with ethyl substituent provided the corresponding acid in considerably lower yield of 16 % (table 3, product **13**). The methyl-substituted analogue (table 3, product **14**) was also formed cleanly and detected with GC-Ms. In contrast, the chloro-substituted internal substrate was not tolerated. Various terminal alkynes provided saturated β-carboxylic acids (table 3, products **15-18)** respectively in the current reaction conditions. Interestingly the aliphatic 1-decyne reacted smoothly affording undecanoic acid (table 3, product **17)** in 25 % yield. In addition, the carboxylation products of cyclohexyl and 1-cyclohexene-alkynes were detected via GC-Ms. The bulky triisopropylsilicon-functionality was not tolerated instead. Most importantly the carboxylation of alkylboranes was functional with both terminal and internal alkyne substrates having different electronic properties.

Table 2. Optimization of the Carboxylic Acid synthesis with phenylacetylene

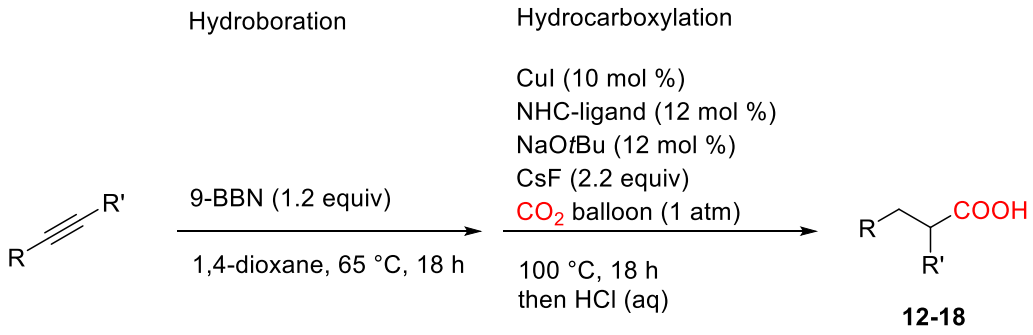


Entry	Catalyst system	Solvent	Equiv of additive (X)	Yield (%)[a]
1.	[IPrCuCl] + *t*BuONa	dioxane	2.2	25
2.	[IPrCuCl] + *t*BuONa	dioxane	3.0	22[b]
3.	[IPrCuCl] + *t*BuONa	THF	2.2	trace
4.	[IPrCuCl] + *t*BuONa	hexane	2.2	trace
5.	[IPrCuCl] + *t*BuONa[c]	dioxane	2.2	24
6.	[IMesCuCl] + *t*BuONa[d]	dioxane	2.2	23
7.	[IPrCuCl]	dioxane	3.0	-
8.	*t*BuONa	dioxane	3.0	-

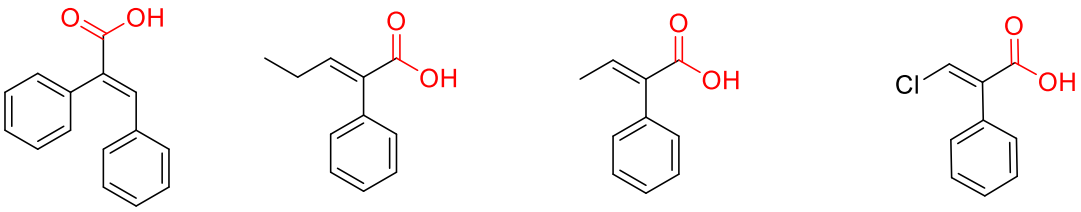
Reaction conditions: Hydroboration: Phenyl acetylene 33 µL (0.30 mmol, 1 equiv), 9-BBN 80 mg (0.36 mmol, 1.2 equiv), 1.5 mL of dioxane. Hydrocarboxylation, IPr ligand 15.3 mg (12 mol %), Na*t*BuO 3.45 mg (12 mol %), CuI 5.8 mg (10 mol %), CsF (X equiv), CO_2 balloon, 1.5 mL of dioxane. Acidic work up with 5 M HCl.

[a] GC yields using acetophenone as internal standard. **[b]** Isolated yield. **[c]** IPrCuCl complex 17.5 mg (12 mol %) **[d]** IMes ligand 12.3 mg (12 mol %).

Table 3. IPrCuF-catalyzed carboxylation of different hydroborated alkynes

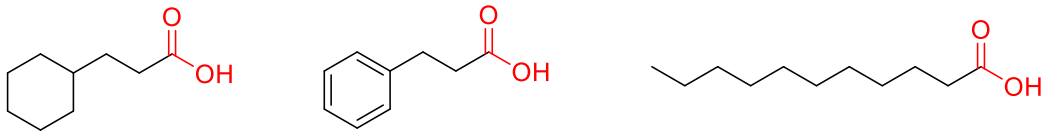


Internal alkynes

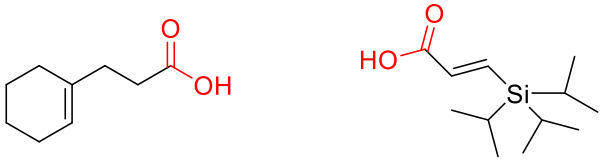


12 45 %[a)] **13** 16 %[a)] **14** crude product [b)] no reaction

Terminal alkynes



15 crude product [b)] **16** 25 % [c)] **17** 25 % [c)]



18 crude product [b)] no reaction

Reaction conditions: Hydroboration: Alkyne (0.30 mmol, 1 equiv), 9-BBN 80 mg (0.36 mmol, 1.2 equiv), 1.5 mL of dioxane. Hydrocarboxylation, IPr ligand 15.3 mg (12 mol %), Na*t*BuO 3.45 mg (12 mol %), CuI 5.8 mg (10 mol %), CsF 100 mg (2.2 equiv), CO_2 balloon, 1.5 mL of dioxane. Acidic work up with 5 M

HCl. a) Isolated yields. b) Product detected via GC methods but not purified. c) GC yields using acetophenone as internal standard.

8. NHC-Copperhydride-catalyzed hydrocarboxylation of alkynes

8.1. Carboxylation procedure 3

The methodology was used successfully for both terminal and internal substrates.

Formation of the catalyst

Imidazolium copper(I) chlorides **5** (15.3 mg, 0.036 mmol, 3.3 mol %) or **6** (12.3 mg, 0.036 mmol, 3.3 mol %) and Na*t*BuO (10.0 mg, 0.104 mmol, 9.5 mol %) were weighted to a 25 mL Schlenk tube equipped with a magnetic stirrer. 2 mL of dioxane was added and the mixture was stirred in the glovebox at rt for 24 hours. Subsequently 100 mg (0.67 mmol, 0.67 equiv) of CsF was added and the stirring was continued for 30 more minutes, then 370 μL (2.00 mmol, 2.0 equiv) of triethoxysilane was added via a syringe affording a bright orange solution immediately, establishing the formation of copperhydride. The hydride lasts in the solution for around 10 minutes before decomposition.

Hydrocarboxylation

To a 25 mL Schlenk tube containing the hydride solution was rapidly added 1.00 mmol (1.0 equiv) of the starting alkyne and the solution was diluted to a total volume of 3.5 mL with dioxane in the glovebox. Then the Schlenk tube was sealed with a rubber septum and taken out of the glovebox. It was evacuated and refilled with a CO_2 for three cycles. Finally, a CO_2 balloon was stabbed through the septum of the Schlenk tube (affording a 1 atm CO_2 atmosphere to the reaction.) The tube was set to a pre-heated oil bath and covered with an aluminium foil. The reaction mixture was stirred for 15 hours at 110 °C.

Work up

The Schlenk tube was cooled down and the solution was transferred to a separation funnel together with 10 mL of Et_2O and 10 mL of saturated aqueous sodium bicarbonate solution,

$NaHCO_3$ (aq). An extraction with $NaHCO_3$ was repeated three times in order to trap the ionic carboxylate product to the aqueous phase. The combined aqueous portions were first washed with 5 mL of Et_2O and then treated with 6 M HCl in a beaker until the solution turned acidic. The aqueous solution was returned to the extraction funnel and extracted three times with 10 mL of Et_2O. The organic phases were collected and dried over Na_sSO_4. After filtration the solvent was removed with a rotary evaporator and the product was then dried under vacuum. The desired carboxylic acids were obtained without purification or the crude products were purified by flash column chromatography to yield the product. 20:1 DCM/MeOH was used as an eluent for primary carboxylic acids. 5:1 Hexane/EtOAc was used as an eluent for 1,2-disubstituted products. The products were obtained as off-white/yellow solid.

8.2. Optimization of the reaction conditions and product scope

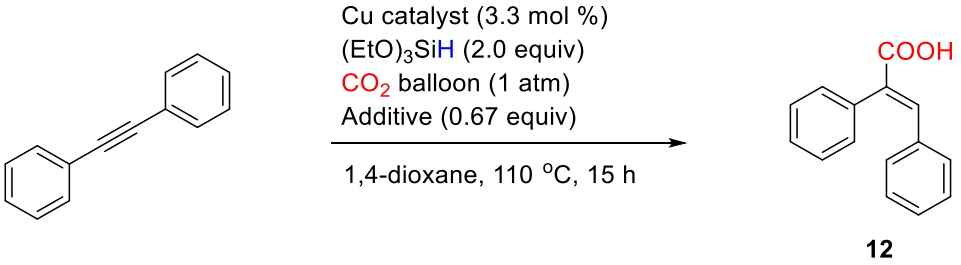
The optimization study for the reaction conditions was done using diphenylacetylene as the starting alkyne, $(EtO)_3SiH$ as the reducing agent, an (NHC)copper catalyst and a CO_2 balloon in a solution of 1,4-dioxane. The reaction produced considerable amounts of *cis*-stilbene as a byproduct lowering the yields of the desired (E)-2,3-diphenyl acrylic acid **12**. This may be caused by an incomplete CO_2 insertion into the alkenyl copper complex (see complex 14b in scheme 9). On the other hand, the direct reduction of the alkyne to the corresponding olefin by the excess of hydrosilane can also be considered to be the source of the byproduct. Similarly, the reaction of terminal phenyl acetylene produced styrene as a byproduct. The formations of the reduced byproducts were detected and characterized with the GC-Ms.

Employing IMesCuCl **5** or IPrCuCl **6** as a precatalyst and sodium *tert*-butoxide as a base, the reaction resulted in only trace amounts of **12** (table 4, entries 2 and 3). In contrast, in the presence of CsF as an additive, **12** was obtained in 10 % and 19 % yields (table 4, entries 5 and 8). Apparently, CsF is needed for the greater formation of the copperhydride. The hydride was observed in the solution immediately after the introduction of the hydrosilane, visible due to the colour change to an bright orange. The colour became darker within 10 minutes indicating decomposition of the hydride, as mentioned above chapter 8.1. Furthermore, a bulkier IPr **4** was more suitable for the catalytic reaction than IMes **2** as an ligand. The yield was reduced to 10 % when replacing $(EtO)_3SiH$ with

$(MeO)_3SiH$ (table 4, entry 6), while $(Me)_3SiH$ did not provide **12** at all (table 4, entry7). Finally**,** the copperhydride-formation was tried by replacing CsF with other additives. Interestingly, KF afforded a comparable hydride yet giving low yield of the product, whereas Cs_2CO_3 afforded an unstable hydride that decomposed quickly (table 4, entries 9 and 10).

The reaction provided stereoselectively the E isomers from both internal (table 5, products **12**-**13**) and terminal alkynes (table 5, products **19**-**25**), this was confirmed by NMR studies and literature sources.[36] Aryl alkynes were mainly obtained with greater yields, but also cyclohexyl and aliphatic substrates provided the corresponding acids (table 5, products **24** and **25**). The obtained yields were relatively low, probably owing to the formation of the byproducts. Gratifyingly, the functional group tolerance was good.

Table 4. Effect of the precatalyst and additive used on the CuH-catalyzed hydrocarboxylation of diphenylacetylene



12

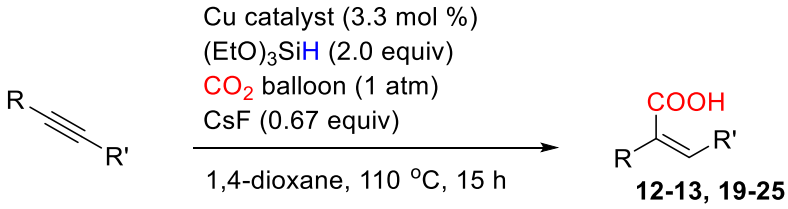
Entry	Catalyst system	Additive	Yield(%)
1.	[IPrCuCl]	-	-
2.	[IPrCuCl] + *t*BuONa	-	trace[a]
3.	[IMesCuCl] + *t*BuONa	-	trace[a]
4.	[IPrCuF][c]	-	-
5.	[IPrCuF] *in situ*[d]	CsF	19[b]
6. [e]	[IPrCuF] *in situ*[d]	CsF	10[b]
7. [f]	[IPrCuF] *in situ*[d]	CsF	-
8.	[IMesCuF] in situ[d]	CsF	10[b]
9.	[IPrCuF] *in situ*[d]	KF	<5[b]
10.	[IPrCuCO$_3$] *in situ*[d]	Cs_2CO_3	-

Reaction conditions: Diphenylacetylene 178 mg (1.00 mmol), hydrosilane 370 µL (2.0 mmol, 2 equiv), NHC-Cu-catalyst (0.030 mmol, 3.3 mol %), NatBuO 10 mg (0.104 mmol, 9.5 mol %), 1,4-dioxane (3.5 mL), CO_2 (balloon), 110 ^{o}C, 15 h. Acidic work up with 6 M HCl.

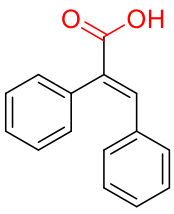
[a] Yields were determined by GC methods **[b]** Isolated yield. **[c]** 17 mg (0.030 mmol, 3.3 mol % IPrCuF complex was used as a catalyst (this compound was not completely purified) **[d]** *In* situ-catalyst was obtained with addition of 0.67 equiv of additive to the stirred solution of IPrCuCl or IMesCuCl (0.030 mmol, 3.3 mol

%) and 10 mg (0.104 mmol, 9.5 mol %) of NatBuO. **[e]** (MeO)SiH was used as a hydrosilane. **[f]** $(Me)_3SiH$ was used as a hydrosilane.

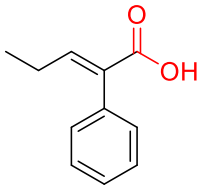
Table 5. IPrCuH-catalyzed carboxylation of different alkynes



Internal alkynes

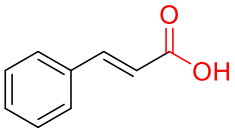


12 19 %

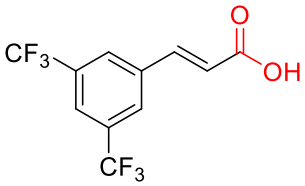


13 18 %

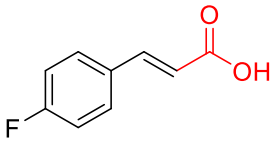
Terminal alkynes



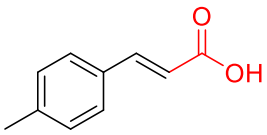
19 19 %



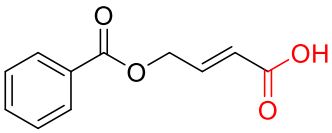
20 11 % a)



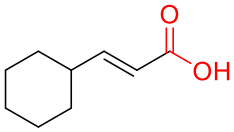
21 9 %



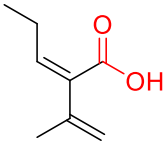
22 21 %



23 7 % a)



24 12 % a)



25 trace a)

Reaction conditions: Alkyne (1.00 mmol), hydrosilane 370 µL (2.0 mmol, 2 equiv), NHC-Cu-catalyst (0.030 mmol, 3.3 mol %), NatBuO 10 mg (0.104 mmol, 9.5 mol %), CsF (100 mg, 0.67 equiv), 1,4-dioxane (3.5 mL), CO_2 (balloon), 110 ^{o}C, 15 h. Acidic work up with 6 M HCl. Isolated yields. a) crude product yield.

9. Boracarboxylation of alkynes with NHC-catalyst

9.1. Carboxylation procedure 4

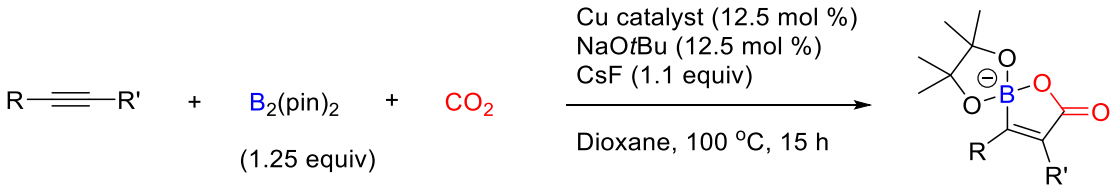
In a glovebox, to a 25 mL Schlenk tube equipped with a magnetic stirrer was weighted 4.6 mg of Na*t*BuO (12.5 mol %) and [NHCCuCl] (12.5 mol %) in 1.5 mL of dioxane. The solution was stirred at rt for 1 h and 67 mg (1.1) of CsF was then added. The solution was stirred for 5 more minutes and subsequently alkyne (0.4 mmol) and 126 mg (0.5 mmol) of B_2pin_2 were added. The volume of the solution was diluted to 3 mL with dioxane. The Schlenk tube was taken out of the glovebox and kept under vacuum for 1 minute. The tube was then opened to a CO_2 (1 atm) for a short while. The reaction mixture was stirred at 100 °C for 15 hours with a CO_2 balloon on it. After cooling to rt, the solution was filtrated, and the solvent was evaporated, until the reaction volume was decreased to 0,5 mL. Subsequently gently heated benzene (1 mL) and ice-cold hexane (20 mL) were added. The resulting solution was kept in the fridge overnight and recrystallization from benzene/hexane was done. Only meager amounts of solid was formed. Absence of four-valent boron signals in ^{11}B NMR studies however, indicated that no product was obtained.

9.2. The reaction scope

The applicability of the *in situ*-formed (NHC)CuF was then investigated for the boracarboxylation of diphenylacetylene and phenylacetylene with $B_2(pin)_2$ as the borane and a CO_2 balloon in 1,4-dioxane (table 6). The catalyst formation was performed similarly with the copper precatalysts **2** and **4**, sodium *tert*-butoxide and CsF, as presented in procedures 1 and 2. The reaction was performed as a one pot-reaction enclosing the hydroboration of the starting alkyne. Instead, the copperfluoride was expected to react with the borane affording [(NHC)Cu-B(pin)] adduct, and subsequent alkyne addition would provide β-boryl alkenylcopper complex (see complexes **43a** and **44a** in Scheme 20

from the literature part). The final CO_2 insertion would provide a cyclic hetero product. The recrystallization of the crude reaction mixture did not however afford the desired product. ^{11}B NMR study revealed only the presence of a three-valent boron (29-32 ppm) indicating the unreacted substrate or other borane byproducts.

Table 6. NHC-copper catalyzed boracarboxylation of alkynes

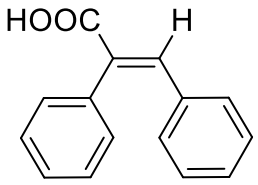


Entry	Catalyst system	Substrate	Additive	Yield(%)
1.	[IPrCuCl] + *t*BuONa	Diphenylacetylene	CsF	not detected
2.	[IMesCuCl] + *t*BuONa	Diphenylacetylene	CsF	not detected
3.	[IMesCuCl] + *t*BuONa	Diphenylacetylene	-	not detected
4.	[IMesCuCl] + *t*BuONa	Phenylacetylene	CsF	not detected
		-		

Reaction conditions: Diphenylacetylene (**1**, 0.40 mmol), copper-catalyst (12.5 mol %), NatBuO (12.5 mol %), $B_2(pin)_2$ (1.25 equiv), additive (1.1 equiv), Dioxane (3.0 mL), CO_2 (balloon), 100 ^oC, 15 h.

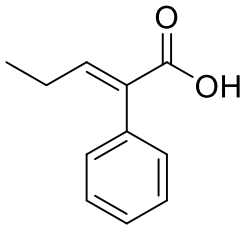
10. Characterization of the products

(E)-2,3-diphenylacrylic acid (12)



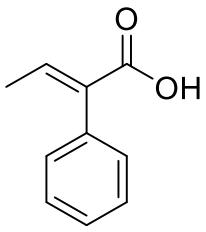
The reaction of diphenyl acetylene afforded the title product following the procedure 2, as an off-white solid (45 mg, 45 %). In comparison, following the procedure 3 the product was obtained as follows: 46 mg, 19 %. ^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm) 7.07 (d, J = 7.3 Hz, 2H), 7.17-7.27 (m, 5H), 7.38-7.44 (m, 3H), 7.96 (s, 1H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ (ppm) 128.07, 128.28, 128.73, 129.51, 129.79, 130.86, 131.62, 134.31, 135.30, 142.48, 173.03.

(E)-2-phenylpent-2-enoic acid (13)



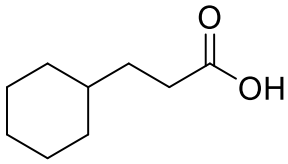
The reaction of but-1-yn-1-ylbenzene afforded the title product following the procedure 2, as an off-white solid (13 mg, 16 %). In comparison, following the procedure 3 the product was obtained as follows: 24 mg, 18 %. The 2D-HMBC-NMR was used to approve the regioisomer. ^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm) 1.05 (t, J = 7.5 Hz, 3H), 2.11-2.19 (m, 2H), 7.19-7.23 (m, 3H), 7.33-7.43 (m, 3H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ (ppm) 13.21, 23.18, 127.33, 128.05, 128.71, 129.38, 129,70, 132.60, 134.69, 149.25, 172.22.

(E)-2-phenylbut-2-enoic acid (14)



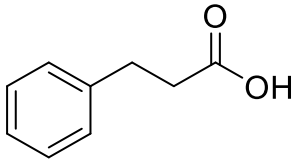
The reaction of prop-1-yn-1-ylbenzene afforded the crude title product (20 mg) following the procedure 2, as an off-white gel-like solid. The crude product was detected by GC. No further purification was done.

(E)-cyclohexyl propanoic acid (15)



The reaction cyclohexyl acetylene afforded the crude title product following the procedure 2, as a yellow gel-like solid (15 mg). The product was detected by GC and crude NMR was recorded. No further purification was done.

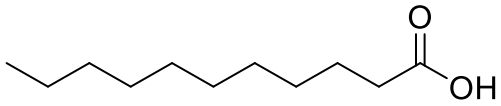
(E)-propanoic acid (16)



The reaction of phenyl acetylene afforded the title product following the procedure 2, as a light yellow solid (10 mg, 22 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 2.73 (t, J = 7.6 Hz, 2H), 3.01 (t, J = 8.1 Hz, 2H), 7.24-7.28 (m, 3H), 7.32-7.36 (m, 2H), 11.34 (bs, 1H).

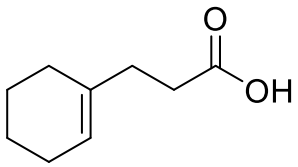
^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 30.63, 35.48, 126.40, 128.28, 128.58, 140.16, 179.31.

Undecanoic acid (17)



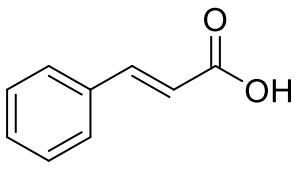
The reaction of decyne afforded the title product following the procedure 2, as a light yellow solid (13 mg, 23 %). ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 0.88 (t, J = 6.7 Hz, 3H), 1.29 (bs, 14H), 1.65 (q, J = 7.4 Hz, 2H), 2.37 (t, J = 7.3 Hz, 2H), 11.42 (bs, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 14.10, 22.68, 24.68, 29.06, 29.24, 29.30, 29.44, 29.55, 31.89, 34.12, 180.47.

(E)-Cyclohex-1-en-1-yl) propanoic acid (18)



The reaction 3-(cyclohex-1-en-1-yl)-propyne afforded the crude title product following the procedure 2, as an off-white gel. The product was detected by GC. No further purification was done.

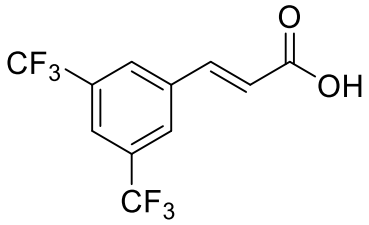
(E)-cinnamic acid (19)



The reaction of phenyl acetylene afforded the title product following the procedure 3, as a light yellow solid (28 mg, 19 %). ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 6.47 (d, J = 15.9

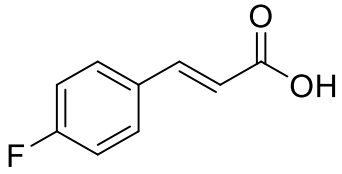
Hz, 1H), 7.42-7.46 (m, 3H), 7.58-7.60 (m, 2H), 7.83 (d, J = 15.9 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 117.17, 128.28, 128.80, 130.69, 134.08, 147.19, 172.05.

(E)-3,5-bis(trifluoromethyl)cinnamic acid (20)



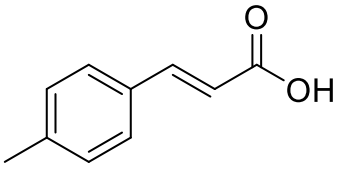
The reaction of 1-ethynyl-3,5-bis(trifluoromethyl)benzene afforded the crude title product following the procedure 3, as an opaque brown solid (15 mg, 11 %). The product was detected with GC and NMR. No further purification was done. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 6.87 (d, 15.7 Hz, 1H), 7.35-7.40 (m, 4 H), 12.48 (bs, 1H).

(E)-3-(4-fluorophenyl) acrylic acid (21)



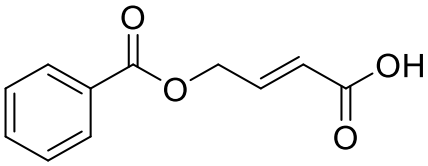
The reaction of 4-fluoro phenyl acetylene afforded the title product following the procedure 3, as an opaque brown solid (10 mg, 9 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 6.41 (d, J = 15.9 Hz, 1H), 7.10-7.19 (m, 2H), 7.55-7.59 (m, 2H), 7.78 (d, J = 16.0 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 116.08, 116.29, 116.83, 130.26, 130.31, 130.34, 145.77, 165.45, 171.32.

(E)-3-(p-tolyl) acrylic acid (22)



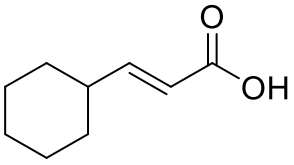
The reaction of p-tolyl acetylene afforded the title product following the procedure 3, as an opaque brown solid (30 mg, 21 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 6.43 (d, J = 16.0 Hz, 1H), 7.24 (d, J = 8.0 Hz, 2H), 7.48 (d, J = 8.1 Hz, 2H), 7.80 (d, 15.9 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 21.53, 116.06, 128.38, 129.71, 131.34, 141.29, 147.10, 172.05.

(E)-4-(benzoyloxy) but-2-enoic acid (23)



The reaction of prop-2-yn-1-yl benzoate afforded the crude title product following the procedure 3, as a yellow gel (10 mg, 7 %). No further purification was done and a crude ^{1}H NMR was obtained. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 3.90 (s, 2H), 6.94 (d, J = 16 Hz 1H), 7.77 (d, J = 16.0 Hz, 1 H), 8.02 (d, J = 11.3 Hz, 2H), 8.12 (t, J = 8.4 Hz, 1H), 8.46 (s, 2H), 12.66 (bs, 1H).

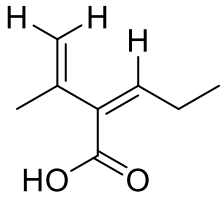
(E)-3-cyclohexylacrylic acid (24)



The reaction of cyclohexyl acetylene afforded the crude title product following the procedure 3, as a yellowish solid (10 mg, 12 %). The product was detected with GC and NMR but no further purification was done. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.11-

1.38 (m, 8H), 1.51-1.63 (m, 2H), 2.15-2.25 (m, 1H), 5.79 (dd, J 0 15.8 Hz, 1H), 7.03-7.09 (q, J = 6.8 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 25.56, 25.89, 26.16, 31.32, 31.52, 40.55, 118.01, 157.37, 171.46.

(Z)-2-(prop-1-en-2-yl) pent-2-enoic acid (25)



2-methylhex-1-en-3-yne afforded the crude title product following the procedure 3, as an off-white gel-like solid in trace amounts. No further purification was done and a crude ^{1}H NMR was obtained. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.06-1.09 (t, J = 7.60 Hz, 3H), 1.93-1.99 (m, 3H), 2.23-2.30 (m, 2H), 4.82 (s, 1H), 5.21 (t, J = 15,7 Hz, 1H), 6.93 (t, J = 7.7 Hz, 1H).

11. Conclusions

Known NHC ligands with an imidazoylidine skeleton were succesfully synthetized, and further on, the corresponding NHC copper(I) complexes were obtained and used as organometal catalysts for the carboxylation of alkynes with CO_2. The relatively stable and air-resistant imidazolium copper(I)chlorides IMesCuCl (**5)** and IPrCuCl (**6)** were used as substrates for the synthesis of the monomeric *tert*-butoxide-, (NHC)Cu*t*BuO (**7-8, 10**) and fluoride carbene complexes, IPrCuF (**11**). According to the previous reports, these two complexes readily activate hydrosilane reagents in order to generate copper(I)hydride catalyst species.

The synthesis and purification of copper(I) catalysts **7**, **8**, **10** and **11** came across comparably challenging due to the significant decomposition of the products. This may be due to the strong anhydrous nature and high air-sensitivity of these complexes. Especially the copper-fluoride is reported to be very unstable in solution and prone to

disproportionation.[36,37] On the other hand, the purification step for the NHC-copper *tert*-butoxides included an acidic celite/silica column that might be inappropriate for the basic NHC ligands.

Consequently, an *in situ*-catalyst formation pathway was chosen to obtain the desired copper fluoride catalysts: The reaction of the initial (NHC)CuCl complex in the presence of *tert*-butoxide base afforded a (NHC)Cu*t*BuO species after stirring in 1,4-dioxane, after which, the corresponding fluorides were obtained after addition of CsF salt. These *in situ*-formed copper fluorides turned out to be crucial for the generation of the NHC-copperhydride species via the reaction with hydrosilane. The introduction of the hydrosilane afforded the formation of copperhydride in the solution, which was detected by an immediate color change to bright orange. The attempts to authenticate the Cu-H peak via ^{1}H NMR however failed, due to the considerably rapid decomposition of the copperhydride. CsF turned out to be the only suitable additive that promoted the formation of the copper hydride in the prevalent conditions.

The *in situ*- produced copper hydrides proved to be an intriguing option for the stereoselective hydrocarboxylation of alkynes with CO_2. According to the NMR study, α,β-unsaturated carboxylic acids were obtained selectively with an E-stereochemistry product from both terminal and internal aryl alkynes. The absence of CsF lead to the formation of the products only in trace amounts. The relatively low yields of the reaction may be explained by the considerable instability of the copperfluoride precatalyst, and copperhydride catalyst in solution, or possible incomplete CO_2 insertion to the alkenylcopper intermediate. Internal aryl alkynes showed slightly increased reactivity compared to the terminal alkynes.

The Copper-catalyzed carboxylation of alkylborane reagents was observed to be another applicable option for the carboxylation of alkynes. The similar *in situ*-generated NHC-copper fluoride catalyst was utilized for this reaction. The employment of CsF was necessary to enhance the σ-bond metathesis reaction between the copper fluoride and the alkylborane species, generated from the starting alkyne upon initial exposure to 9-BBN. 1.2 equivalents of 9-BBN dimer were used for the hydroboration step at elevated temperatures in a 1,4-dioxane solution. Gratifyingly, the tandem hydroboration-carboxylation strategy yielded carboxylic acids from both internal and terminal alkynes in modest yields, including aliphatic alkyne substrate, such as 1-decyne. Interestingly, the internal alkynes provided (E)-α,β-unsaturated products similarly to the reaction catalyzed by the copper hydride, whereas the terminal substrates afforded regioselectively saturated

β-acids. The reason for this may derive from the steric factors of the substrates. Most probably the hydroboration stops at the monoaddition step in the case of disubstituted aryl alkynes. Additional studies on the optimization of the both carboxylation pathways, and applications would be the facile for future studies.

III. Summary

The Copper hydrides used in this work are highly chemoselective reducing agents for a wide range of transition metal-catalyzed transformations. The great electron donating nature of the NHC ligands can be employed to enhance the reactivity of the copper hydride and allow the catalyst loading to be significantly low. The hydrocarboxylation of alkynes has generally required a nickel(0) catalyst with strong and moisture sensitive reducing agent, such as $AlEt_3$ and $ZnEt_2$. The easily handled hydrosilanes offer a milder hydrocarboxylation protocol together with (NHC)copper(I) catalyst. In the optimized conditions the competing hydrosilylation or silacarboxylation reactions can be overcome. The employment of fluorides is known to activate organosilanes. Thus, the catalytically active copper hydride species can be generated *in situ*, when the (NHC)CuF complex is gained through hydrosilane, such as $(EtO)_3SiH$. The alkyne and CO_2 are enabled for insertion into the copper hydride leading to carboxylation. The hydrosilane regenerates the catalyst via σ-bond metathesis.

As a continuum to the previous reports, the copper hydride-catalyzed hydrocarboxylation methodology was extended to a variety of terminal alkynes, and an *in situ*- alternative for the unstable copper fluoride was developed in this experimental study. According to the experimental results and literature, the presence of the fluoride is required for the robust hydride formation and carboxylation while the (NHC)Cu*t*BuO catalyst species seems to have a lower hydrosilane-activating capacity. The NHC ligands probably enhance the stability of the copper(I)fluoride complex and enable solubility in anhydrous solvents.

The electron-rich internal diaryl alkynes apparently show greater reactivity in comparison to the alkyl substituted aryl alkynes or terminal alkynes. The reasons for the lower yields among the terminal substrates, are most probably from the poorer reactivity towards the

copper hydride species, which rapidly decompos in the reaction media. The formation of reduced byproducts, such as *cis*-stilbene and styrene derivatives also reduce the obtained yields. In comparison, Fujihara *et al* reported that an aliphatic internal 5-decyne did not show reactivity at all. Likewise, the (NHC)copper catalysts can be considered to enhance the acidity of the terminal alkynes via acting as a Lewis acid and forming a π-complex with the alkynes.

Another intriguing carboxylation pathway employing NHC-copper complexes with CO_2 utilizes widely and readily available alkylborane reagents. A tandem copper-catalyzed hydroboration-carboxylation methodology has been previously reported for terminal and disubstituted olefins, as well as terminal alkynes in the presence of a suitable base additive. In the current experimental part, the methodology was extended to internal alkynes producing synthetically useful trisubstituted olefins with modest yields. In addition, a range of different terminal alkynes were reacted, probably the most interesting of which was the aliphatic nonarylated 1-decyne. In comparison to the study of Skrydstrup *et al*, the formation of malonic acids from terminal alkynes remained futile, probably due to the incomplete CO_2 insertion, yet producing the corresponding saturated β-acids. The initial hydroboration of the alkyne plays a key due to the copper-catalyzed carboxylation of the alkylborane reagent in the subsequent step.

The mild CsF serves as a compatible alternative for the strong bases used within the cross-coupling reactions occupying organoboron reagents. The effect of the CsF can be related to the promotion of the transmetalation between copper and boron. It can be suggested that the enhancement of the transmetallation proceeds through a four-coordinate boronate intermediate, increasing the nucleophilicity of the alkylcopper species prior to the insertion of CO_2. Similar interaction has been reported within aryl rhodium species and CsF, and with the employment of alkoxide bases. Possible participation of CsF to the carboxylation via fluorocuprate cannot be excluded either. The mechanism is however not confirmed.

Finally, the (NHC)copper-catalysts can be used for heterocarboxylation of alkynes with CO_2 employing $B_2(pin)_2$ as the organoborane reagent. The reaction is reported to provide synthetically useful multifunctionalized olefins, such as β-boralactones. The monomeric, two coordinate copper *tert*-butoxide complex readily undergoes a σ-bond metathesis with

$B_2(pin)_2$ followed by sequential alkyne and CO_2 insertions. The interaction of the oxygen atom of the carboxylate moiety and the boron atom of the B(pin) species, provides the formation of the heterocyclic structure. The *in situ*-NHC-copper fluoride adduct utilized in this experimental study, was however not consistent with this approach. 9-BBN is more acidic compared to the $B_2(pin)_2$. Probably a delicate balance between the basicity of the base additive used and the acidity of the diborane is required for the σ-bond metathesis to proceed.

Considering the reductive carboxylation reactions in common, it is plausable that the degree of Lewis acidity of the alkyne should encounter the Lewis basicity of the base in a suitable relation, to enhance the protonation of the alkyne and the regeneration of the catalytically active copper species.

All in all this work showed that (NHC)copper(I) catalysts can be used for the activation of sp hybridized carbon atoms of alkynes prior to the new C-C bond formation via CO_2 incorporation, resulting in carboxylic acids. Another prominent methodology entails hydroboration-carboxylation sequence in which alkylboranes are carboxylized with CO_2, catalyzed by (NHC)copper complexes.

IV. References

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V. Supporting spectra

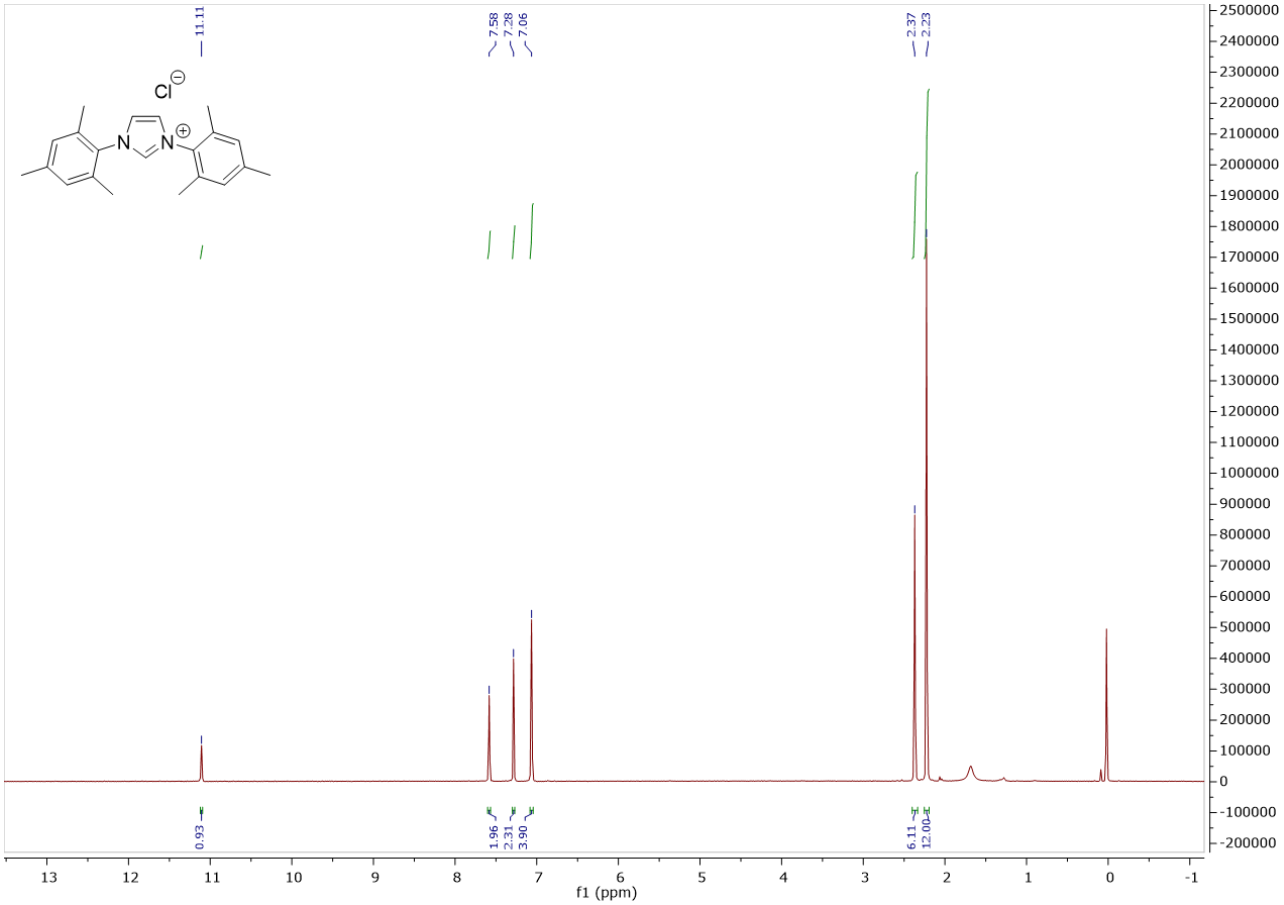


Figure E7: NMR spectrum for compound **2**.

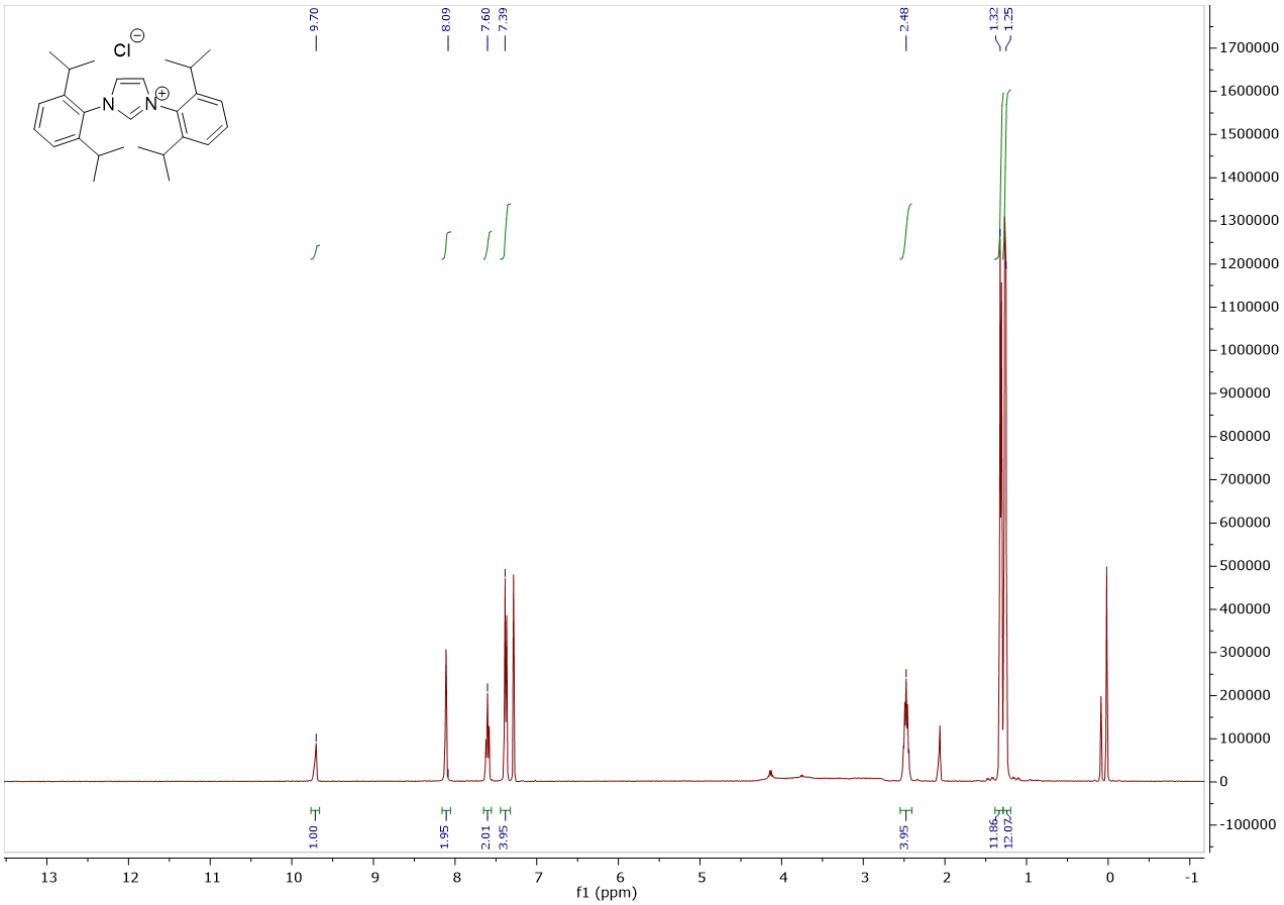


Figure E8: NMR spectrum for compound **4**.

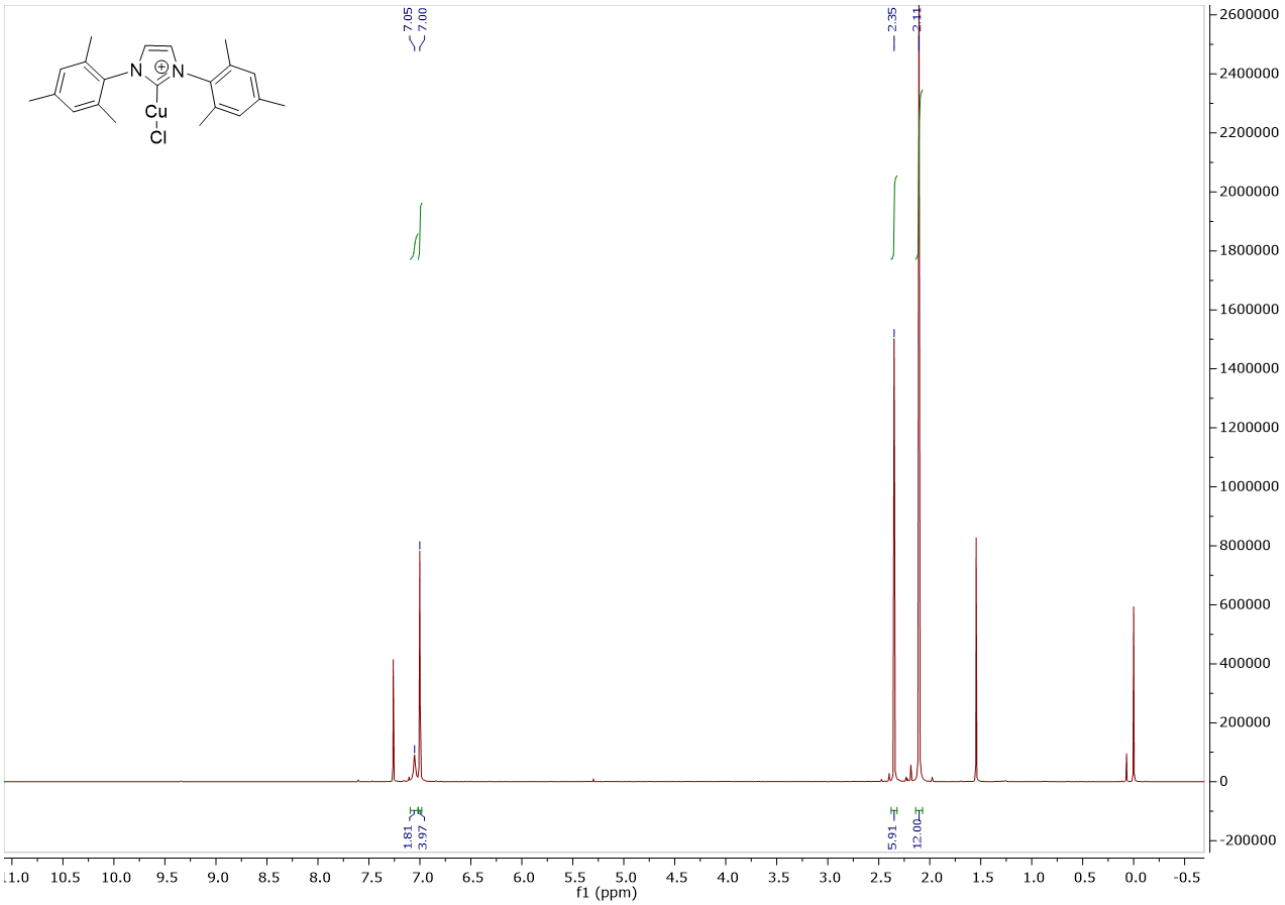


Figure E9: NMR spectrum for compound **5**.

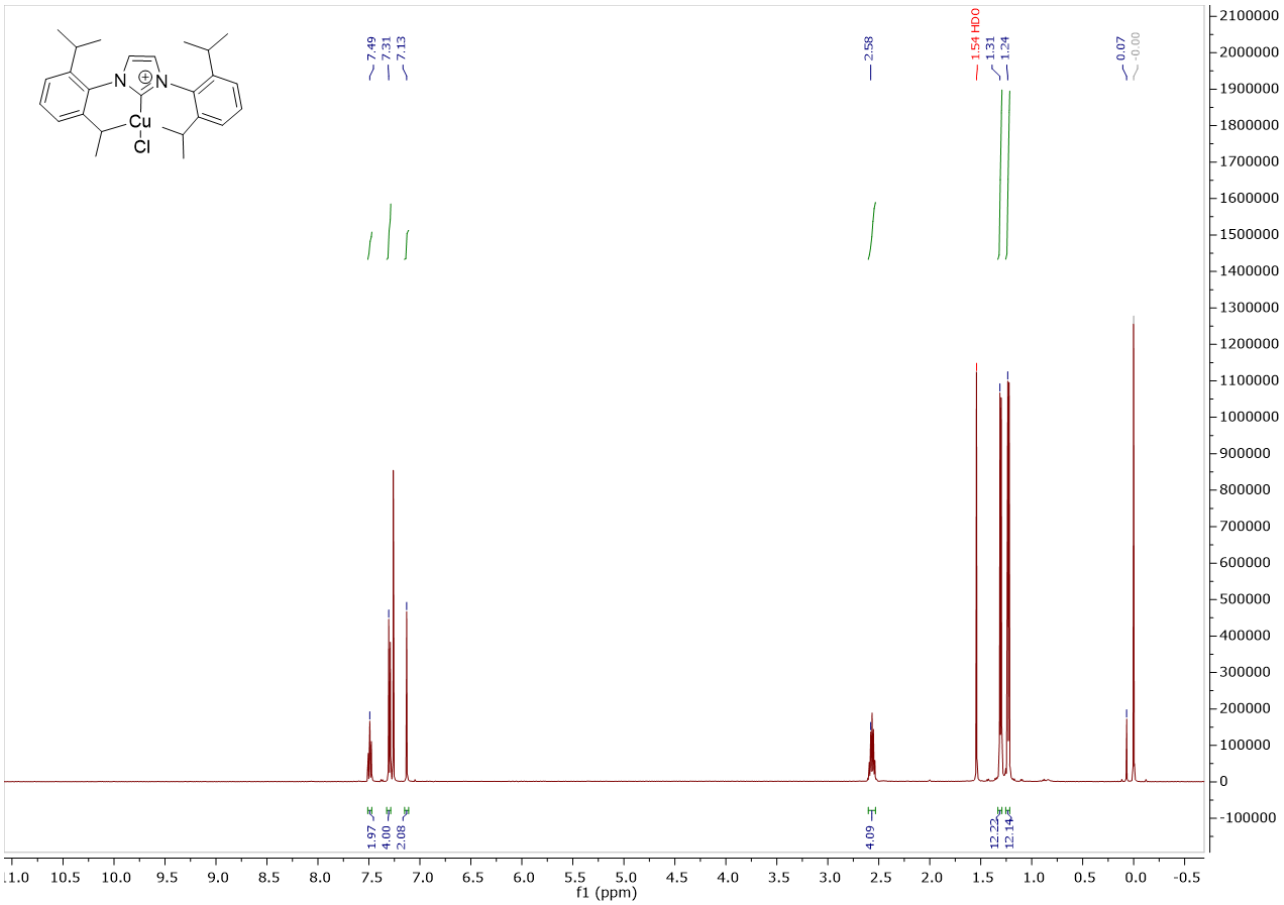


Figure E10: NMR spectrum for compound **6**.

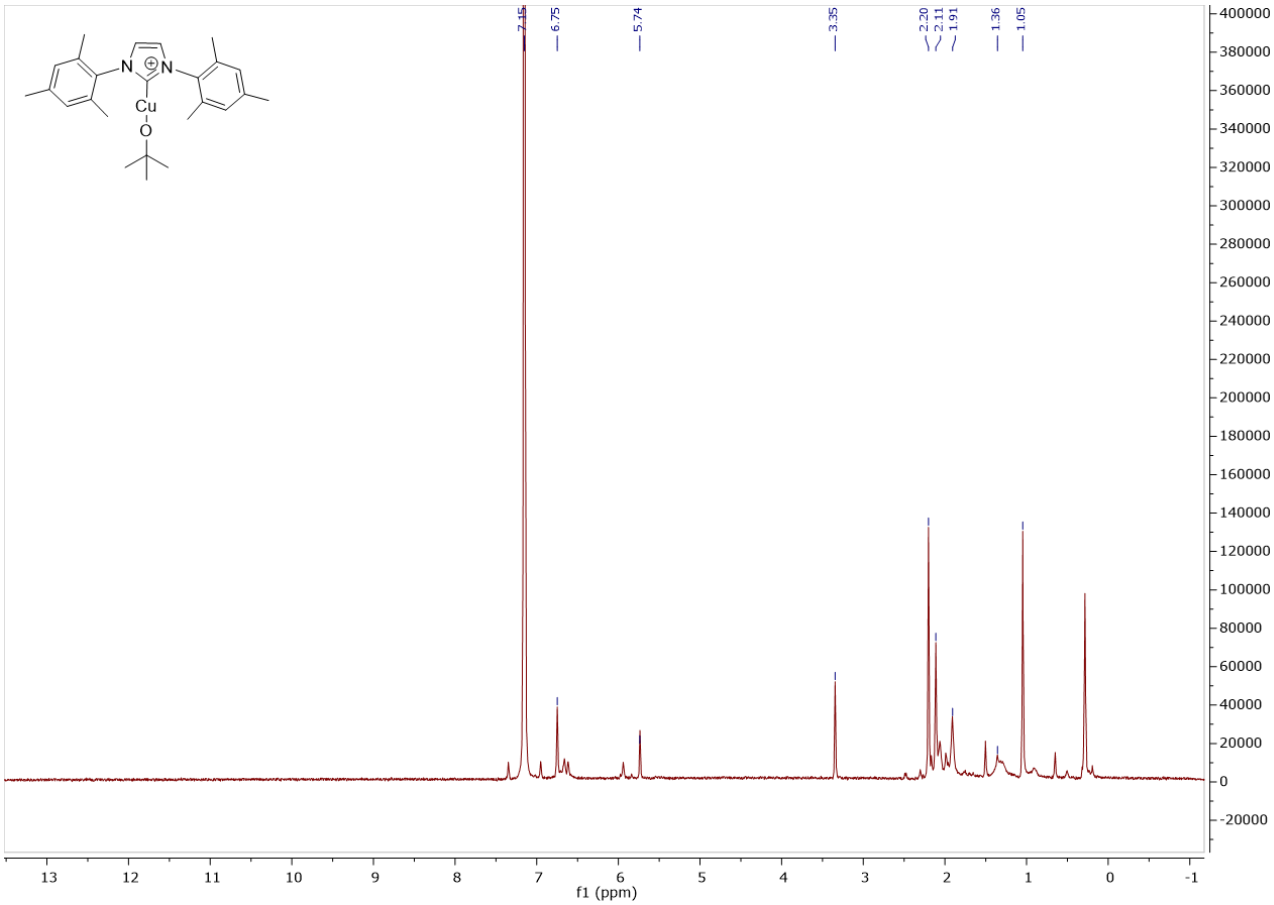


Figure E11: NMR spectrum for compound **7**.

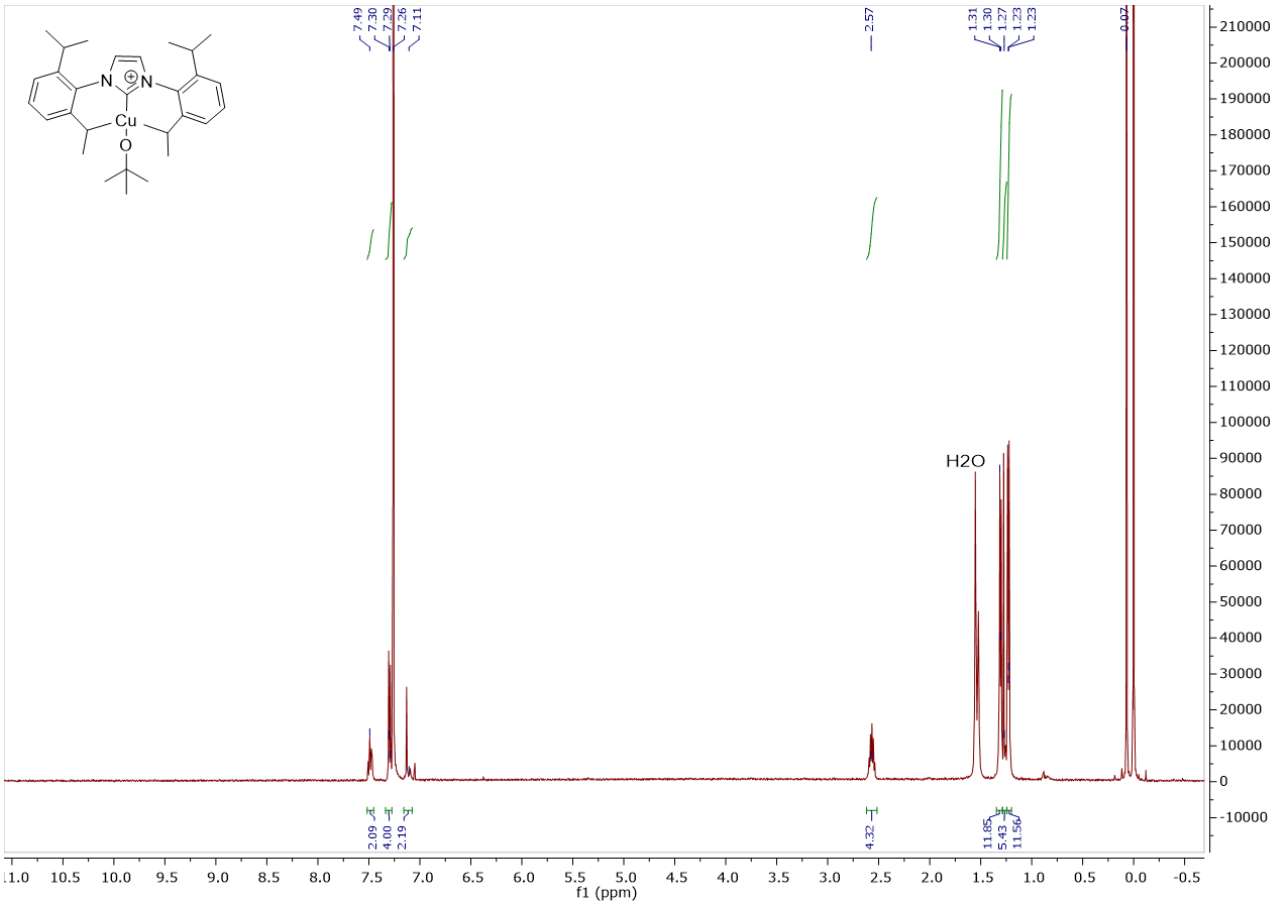


Figure E12: NMR spectrum for compound **8**.

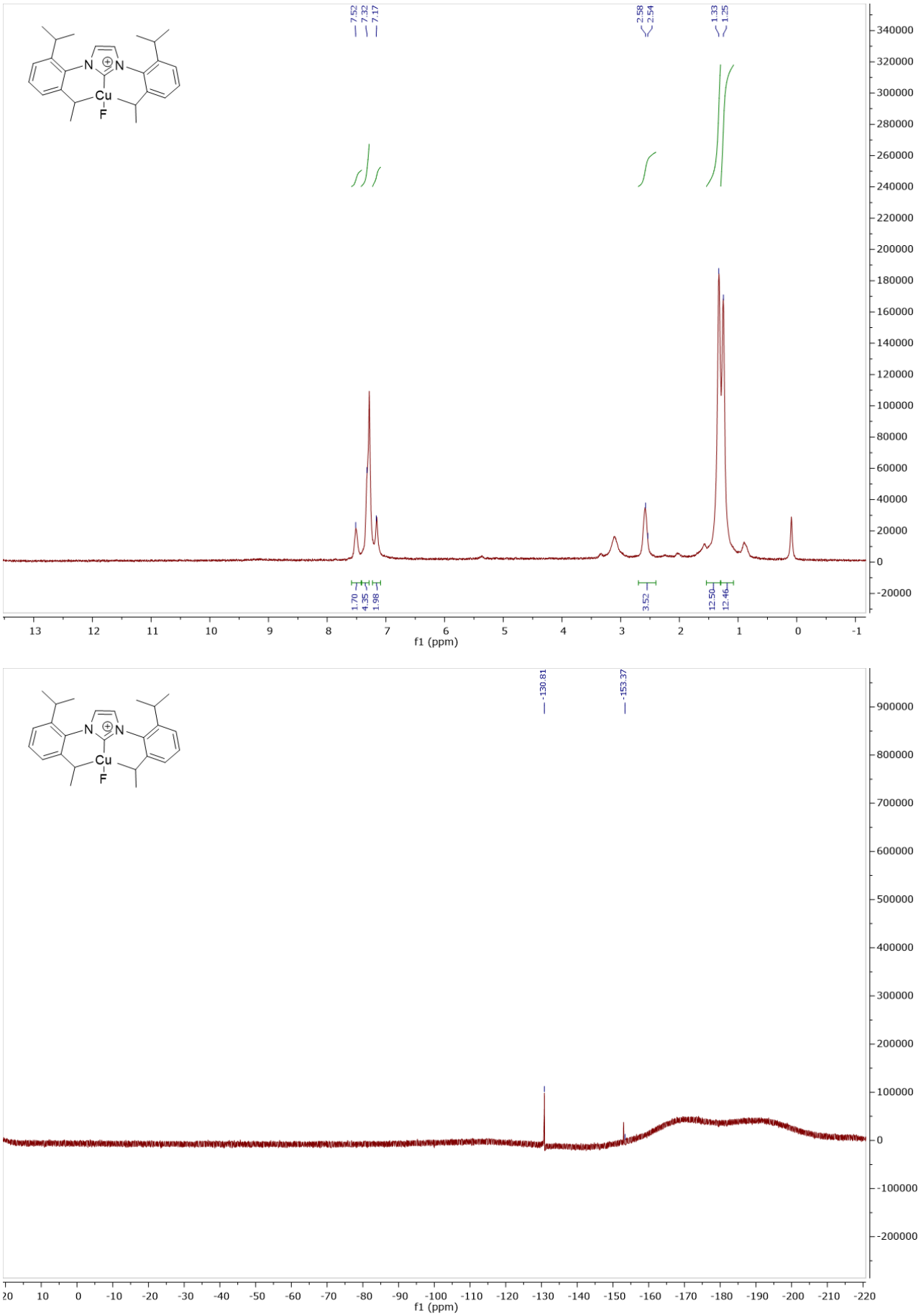
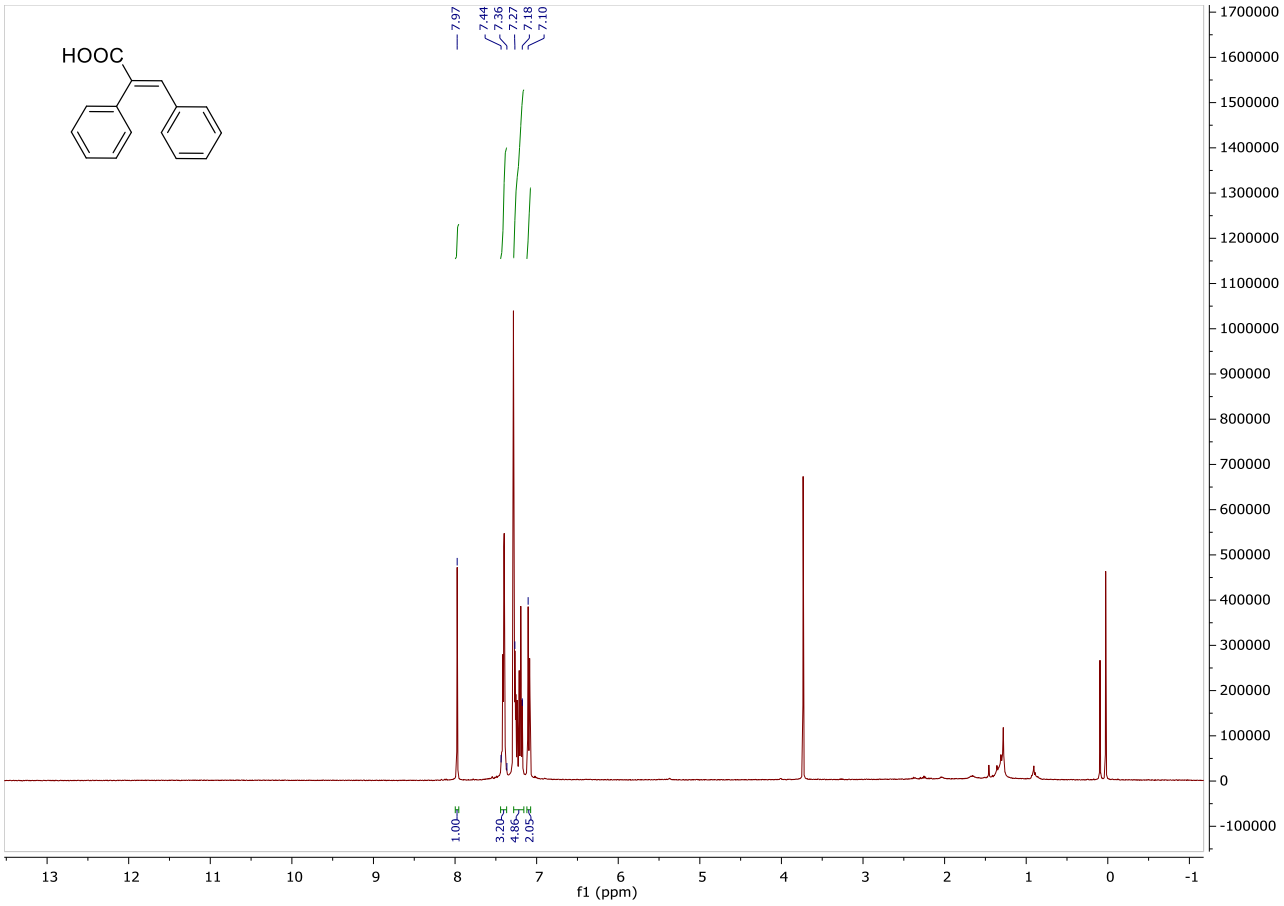


Figure E13: NMR spectra for compound **11**.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7.27
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7.10
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2.05
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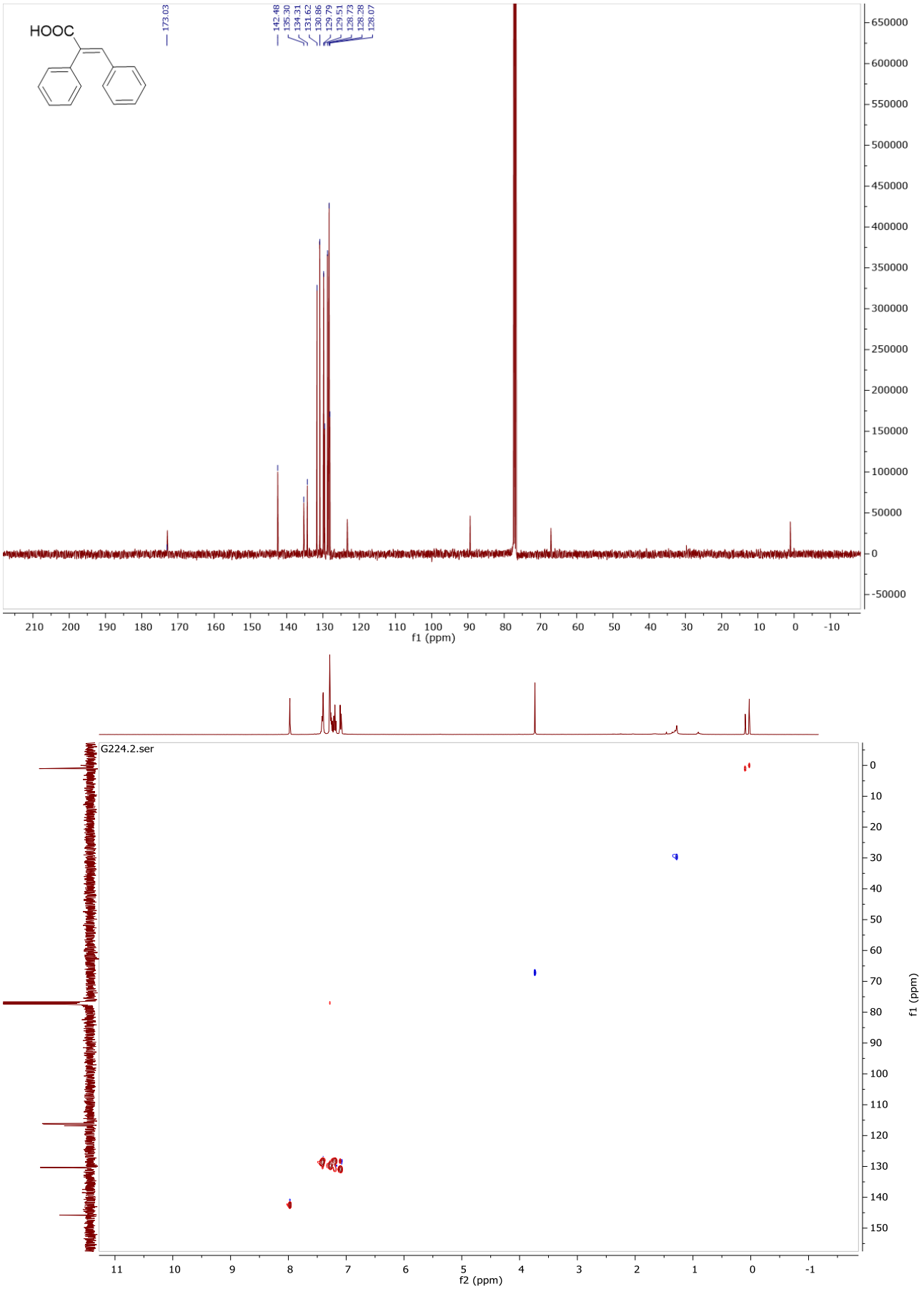
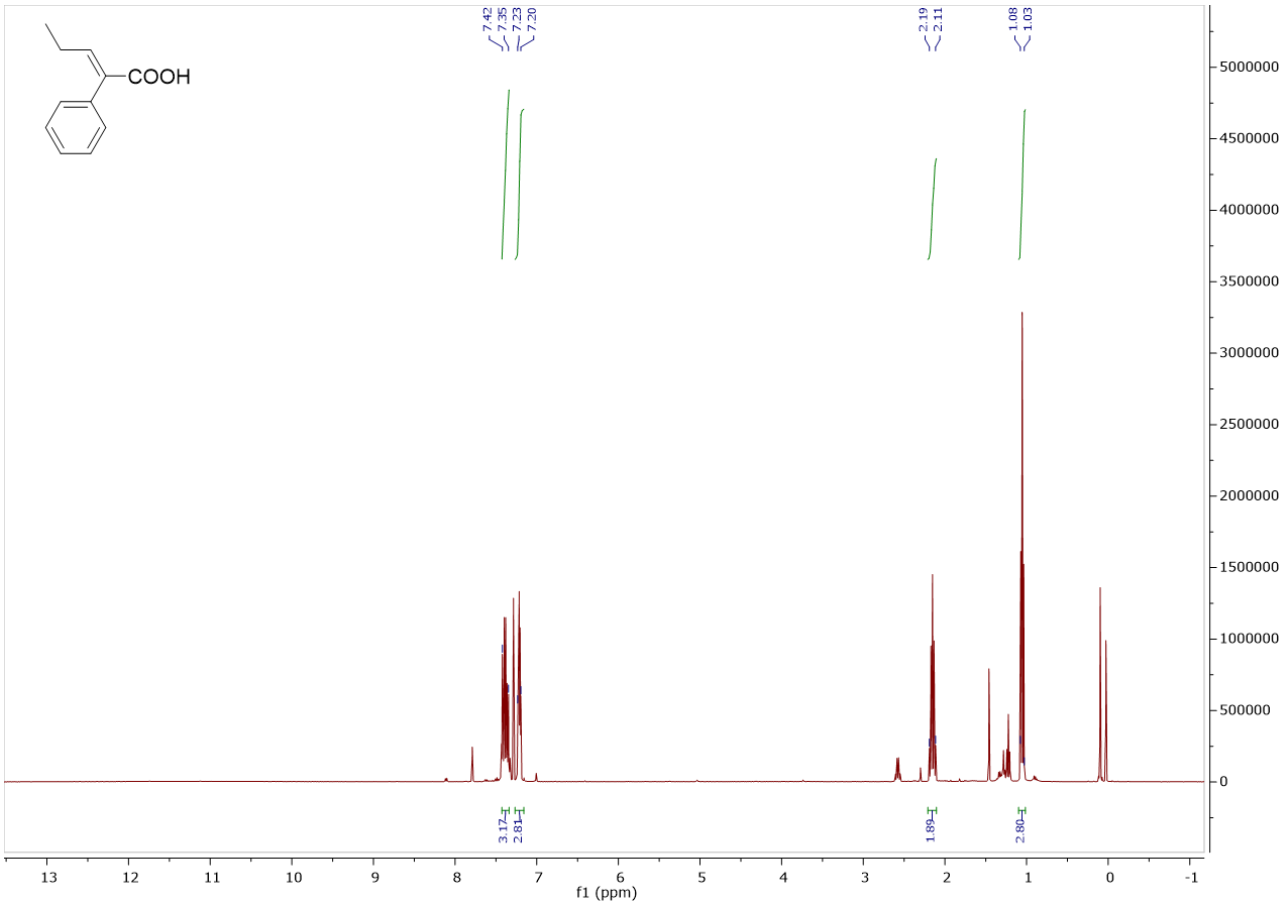
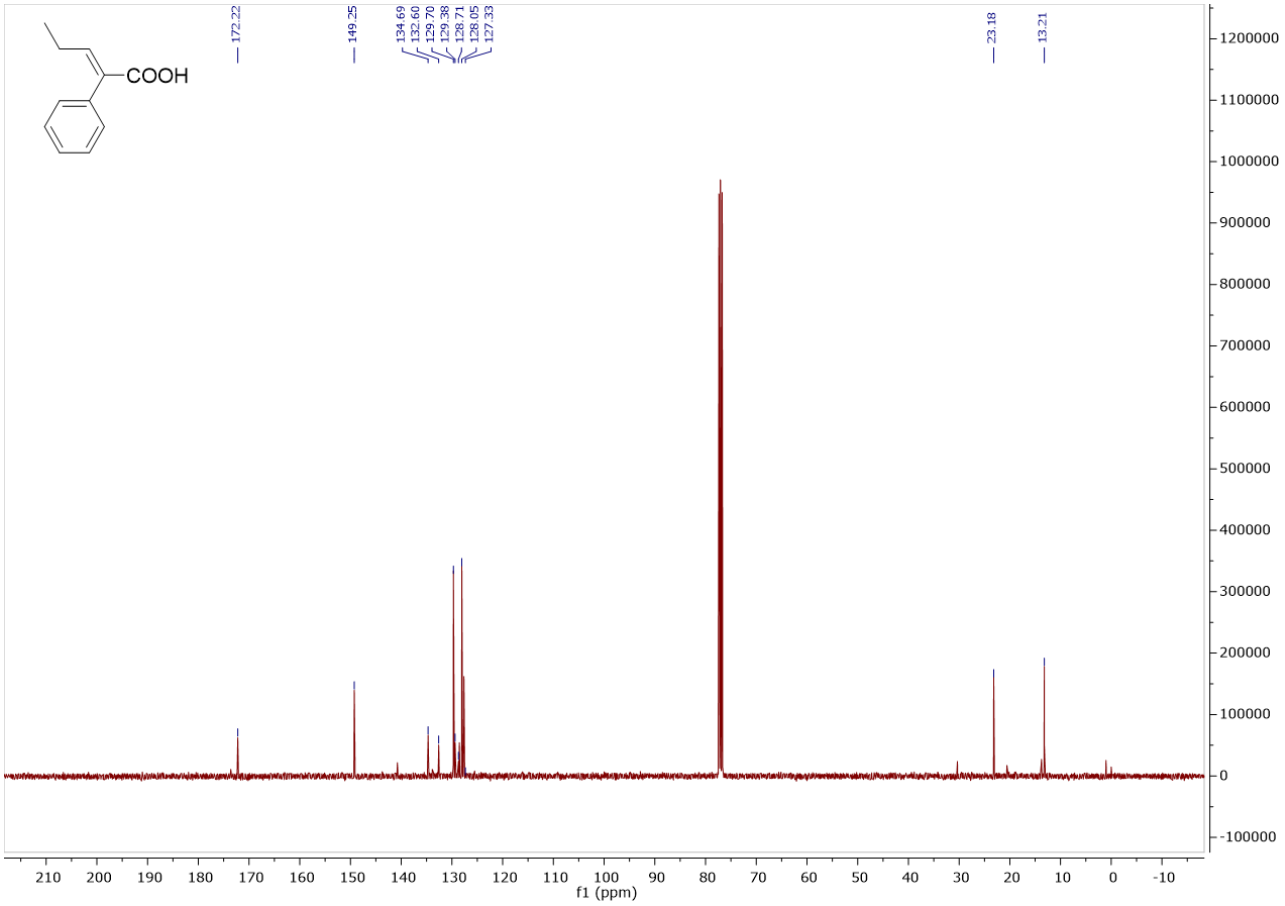


Figure E14: NMR spectra for compound **12**.


COOH
7.42
7.35
7.23
7.20
2.19
2.11
1.08
1.03
3.17
2.81
1.89
2.80
f1 (ppm)


COOH
172.22
149.25
134.69
132.60
129.70
129.38
128.71
128.05
127.33
23.18
13.21
f1 (ppm)

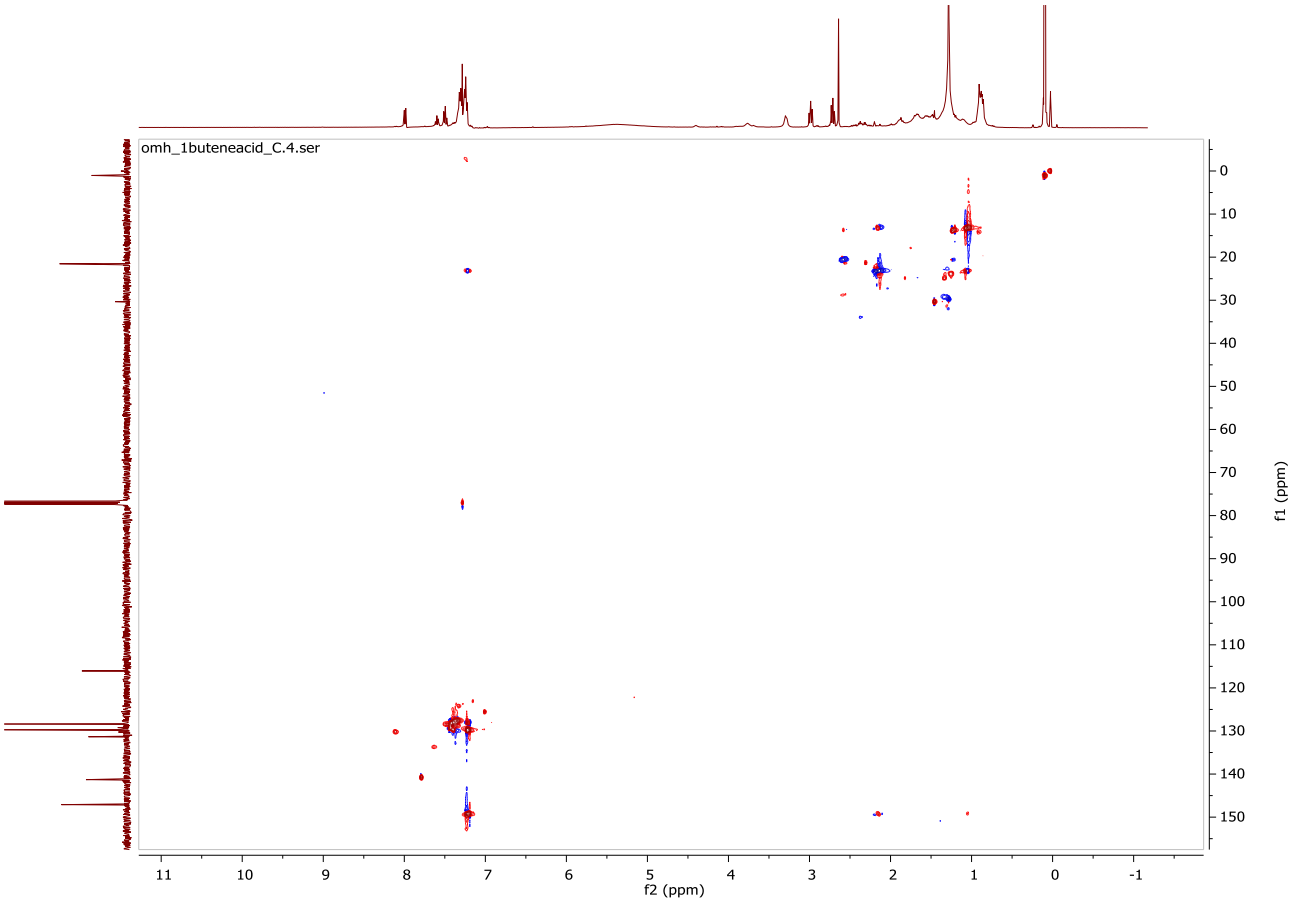


Figure E15: NMR spectra for compound **13**.

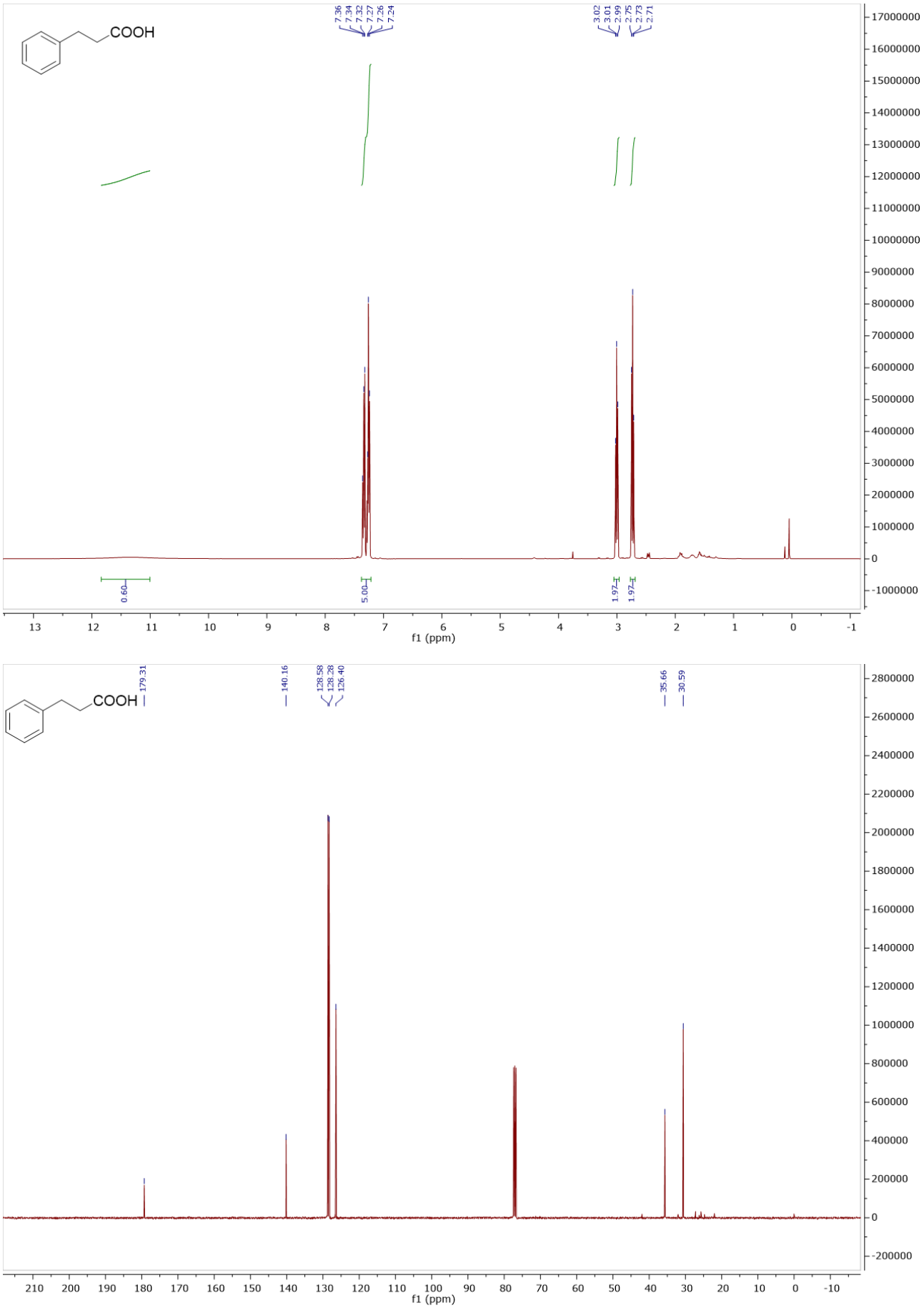


Figure E16: NMR spectra for compound **16**.

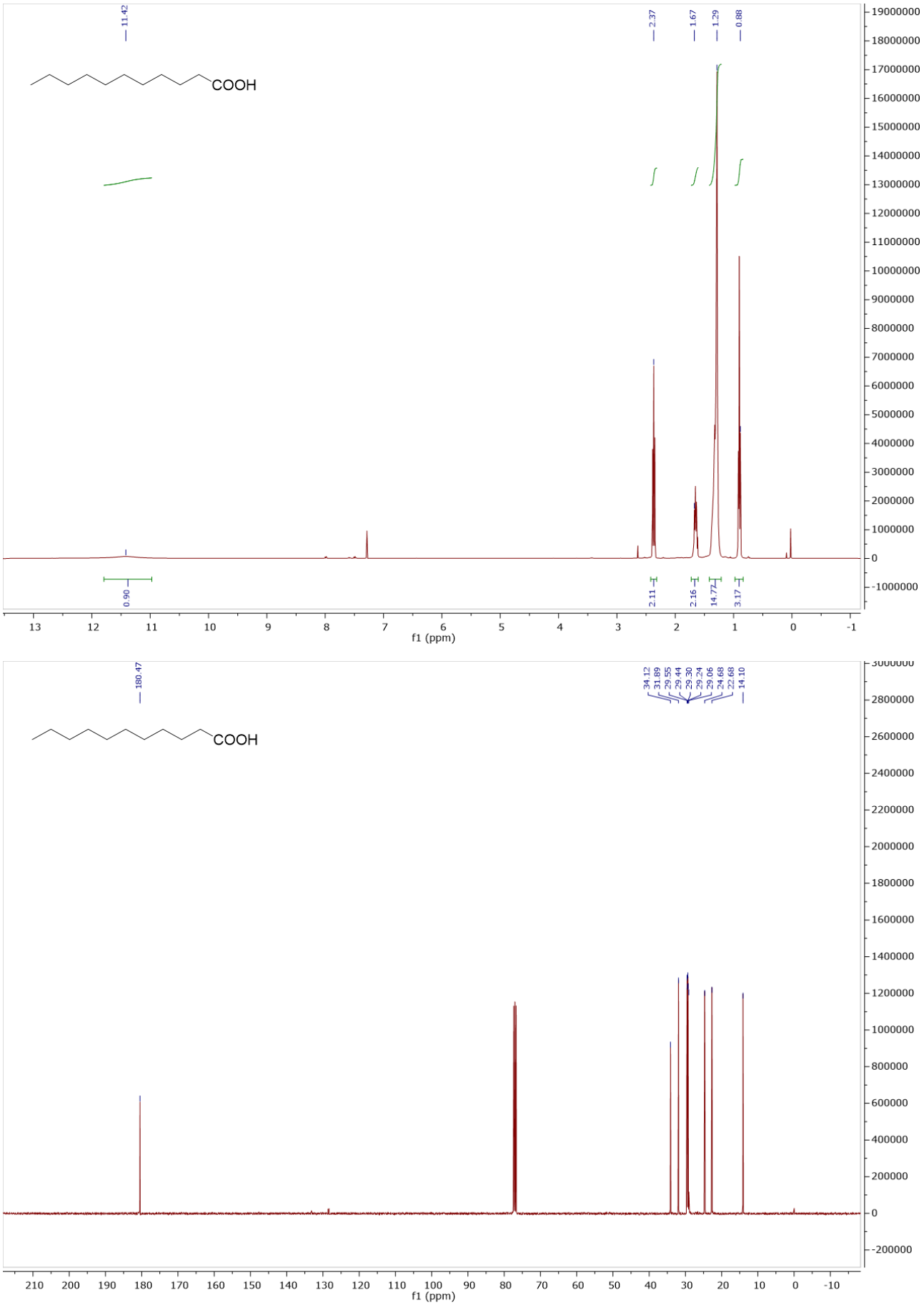
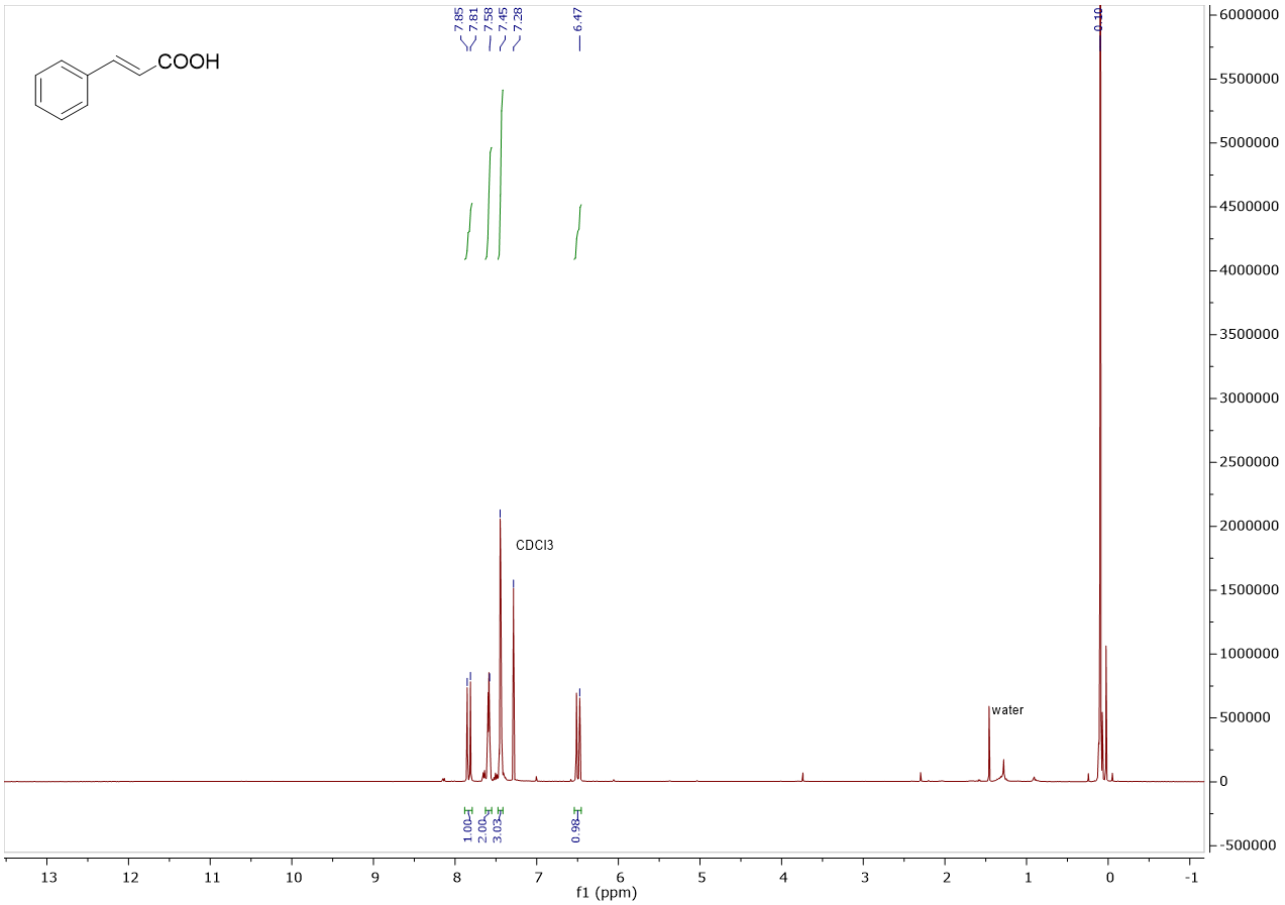


Figure E17: NMR spectra for compound **17**.



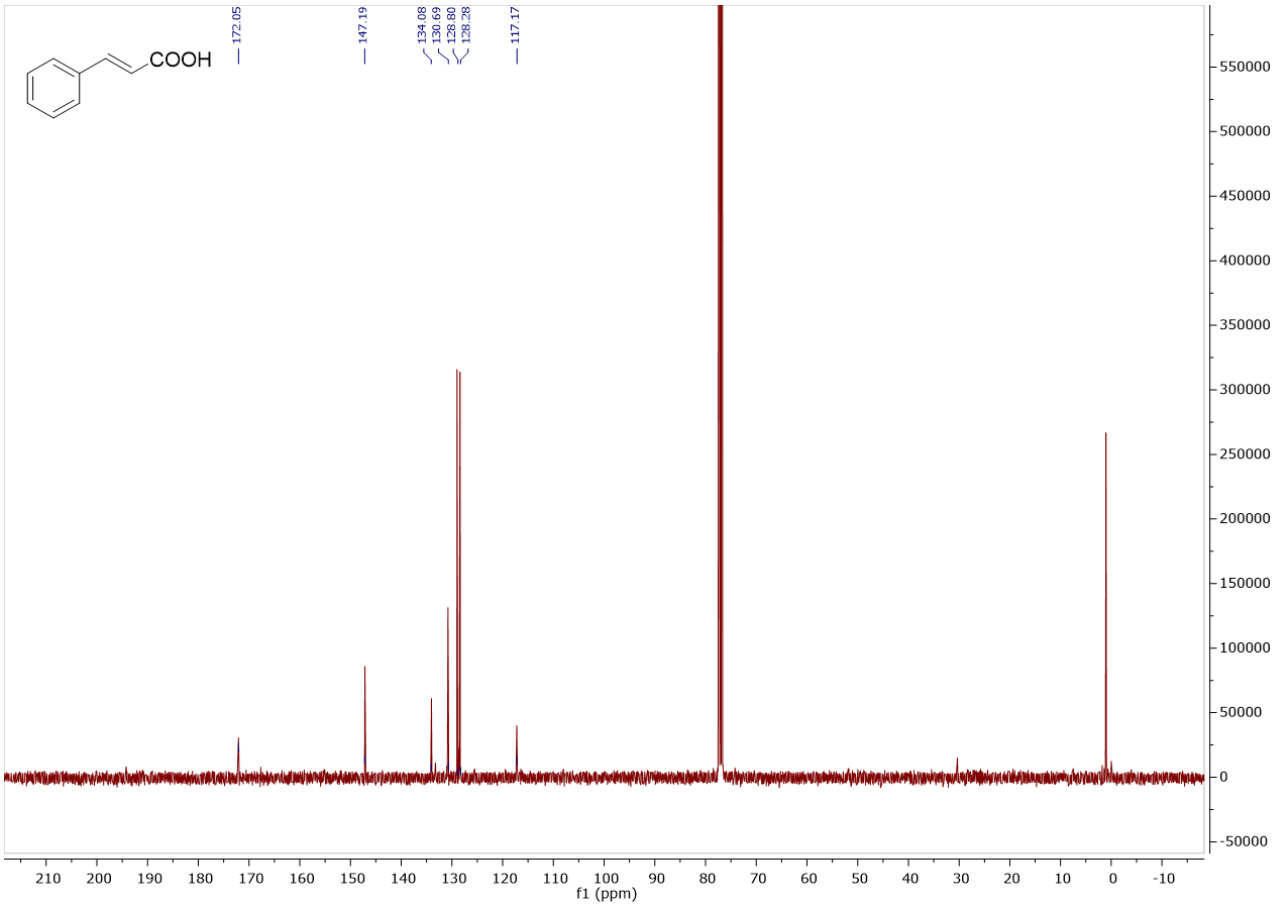


Figure E18: NMR spectra for compound **19**.

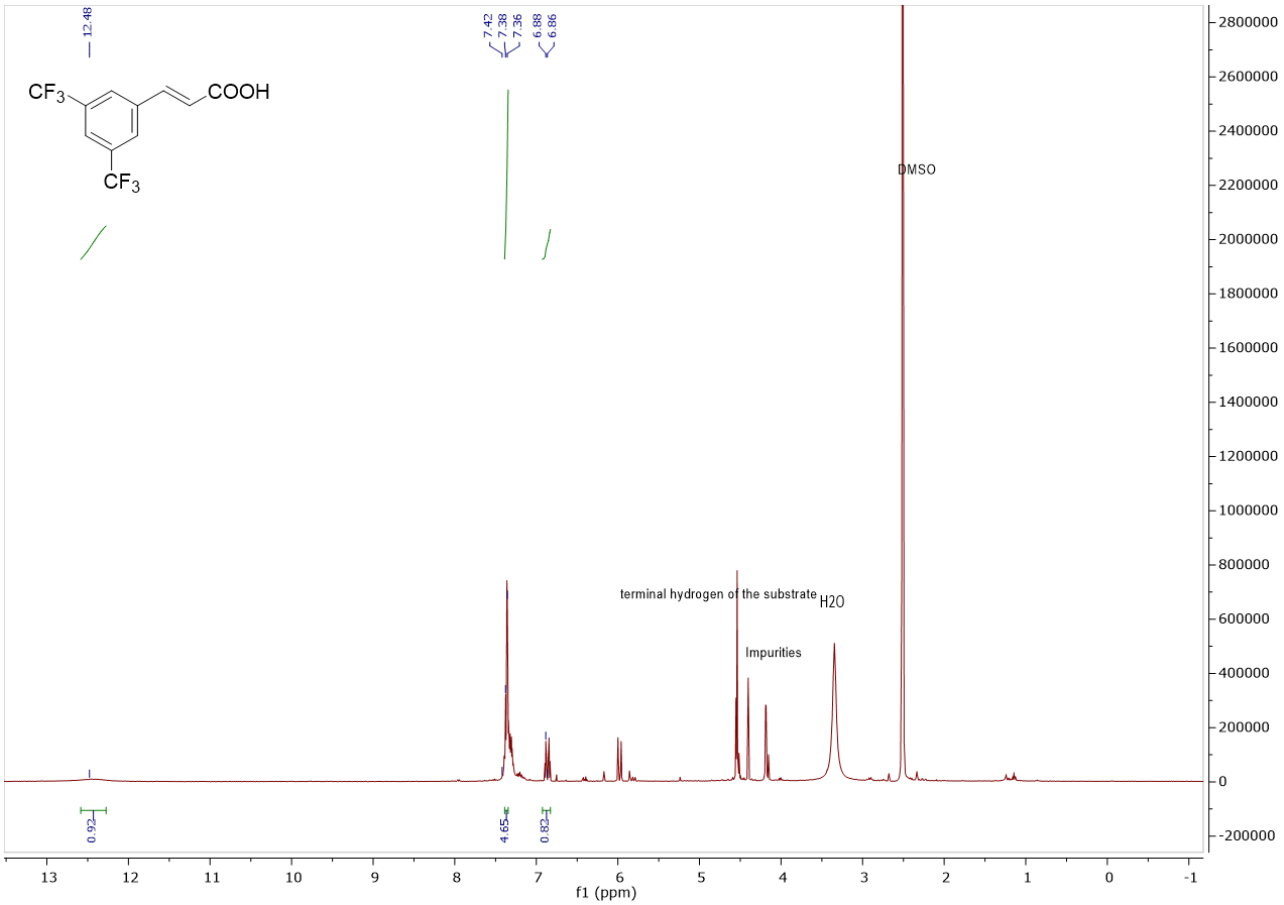


Figure E19: NMR spectrum for compound **20**.

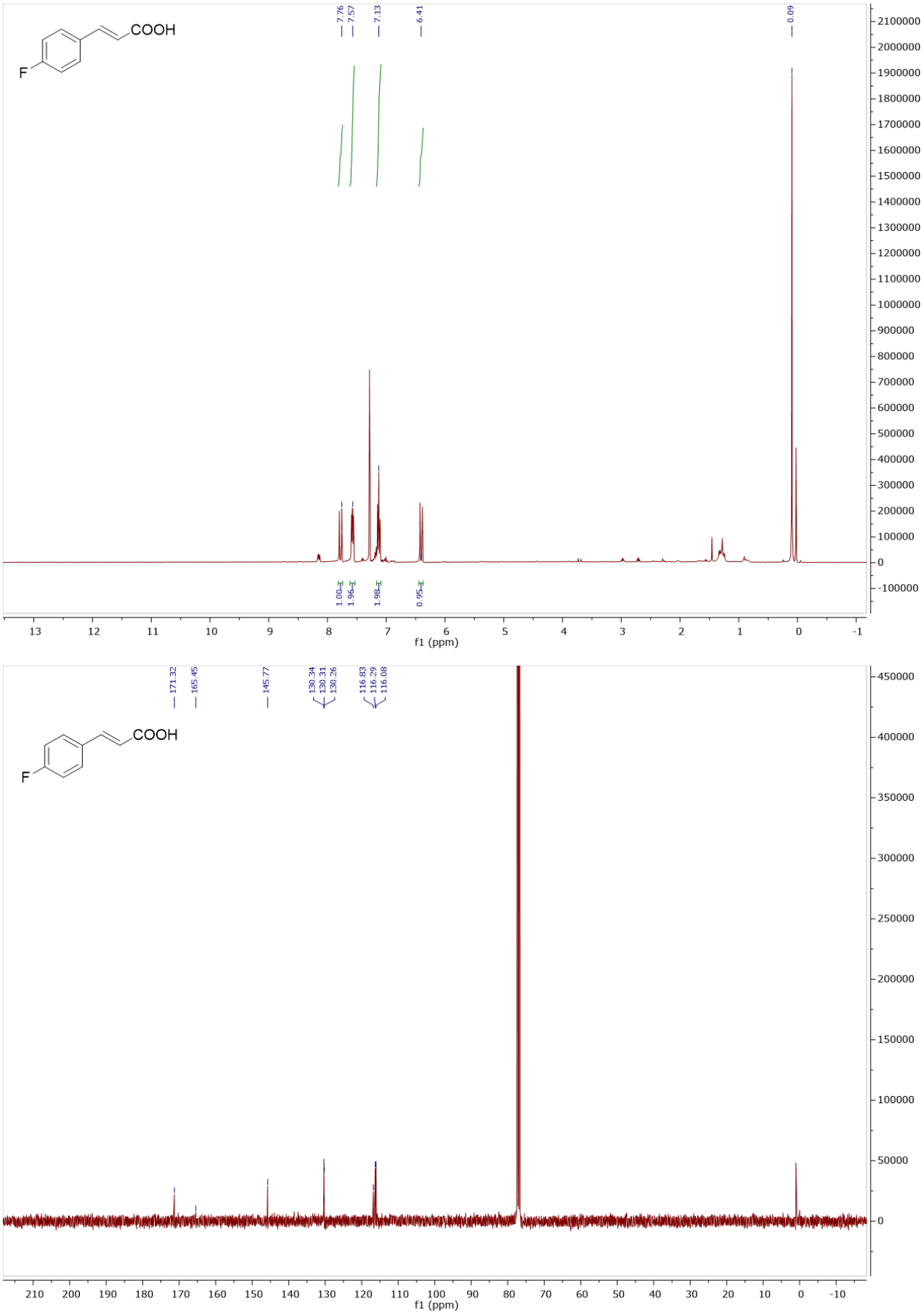


Figure E20: NMR spectra for compound **21**.

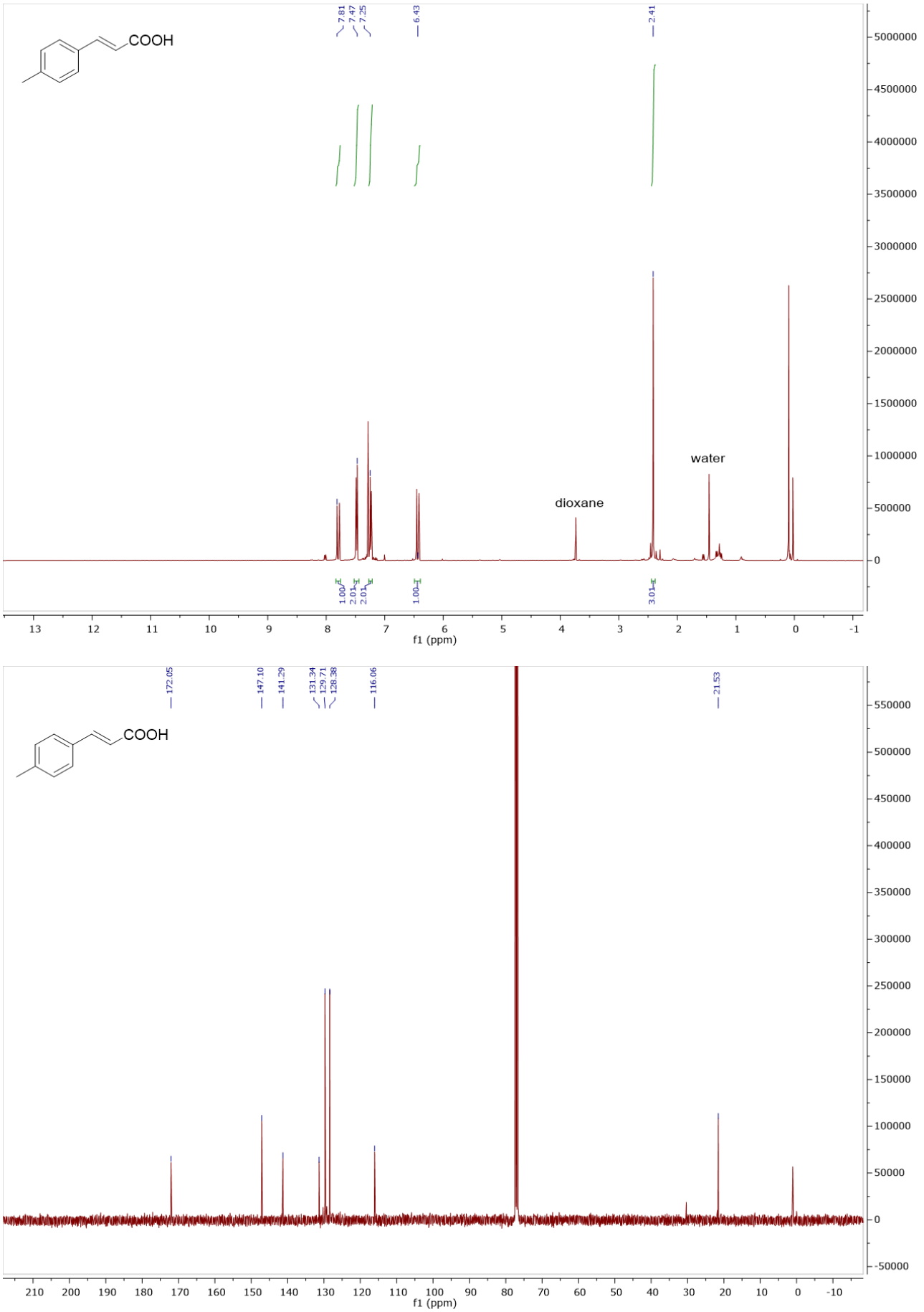


Figure E21: NMR spectra for compound **22**.

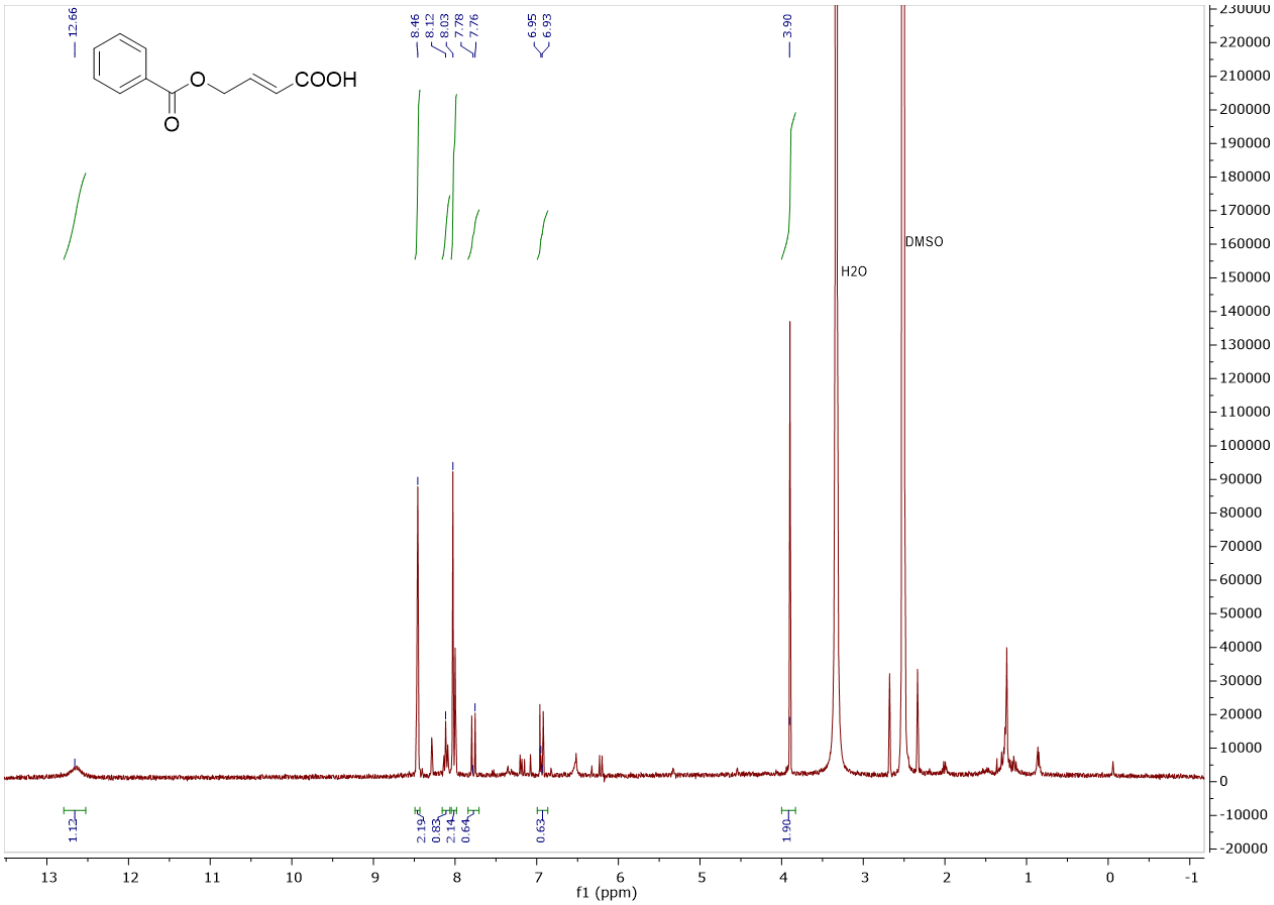


Figure E22: NMR spectrum for compound **23**.

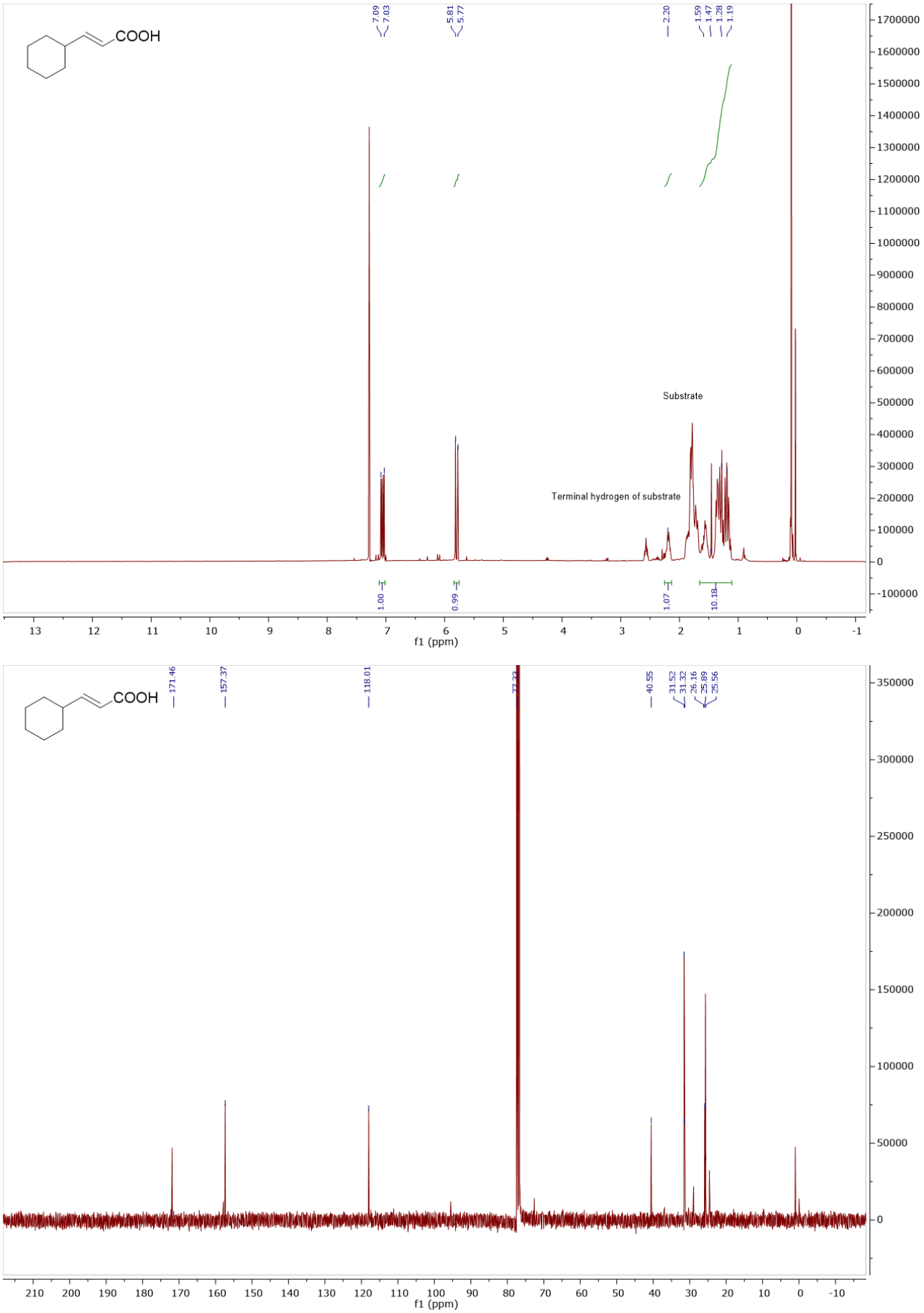


Figure E23: NMR spectra for compound **24**.

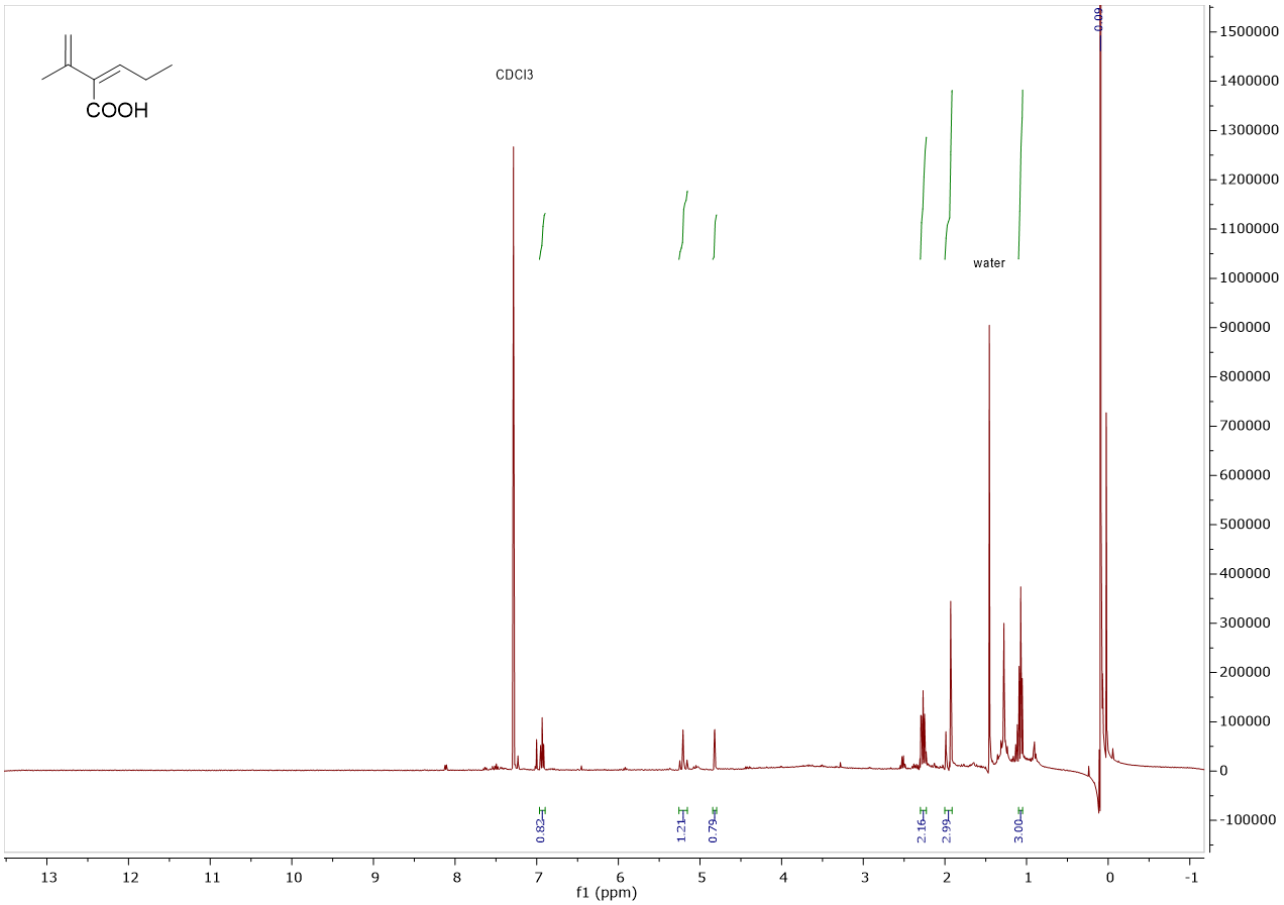


Figure E24: NMR spectra for compound **25**.

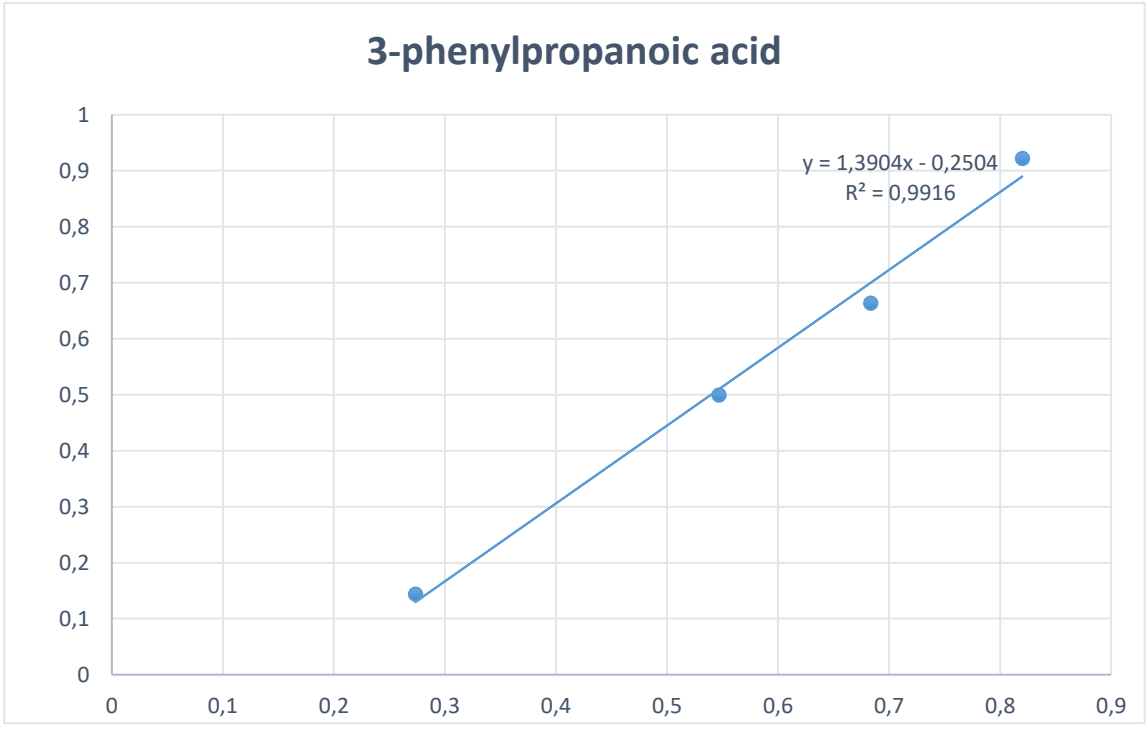


Figure E25: Calibration curve for compound **16.**

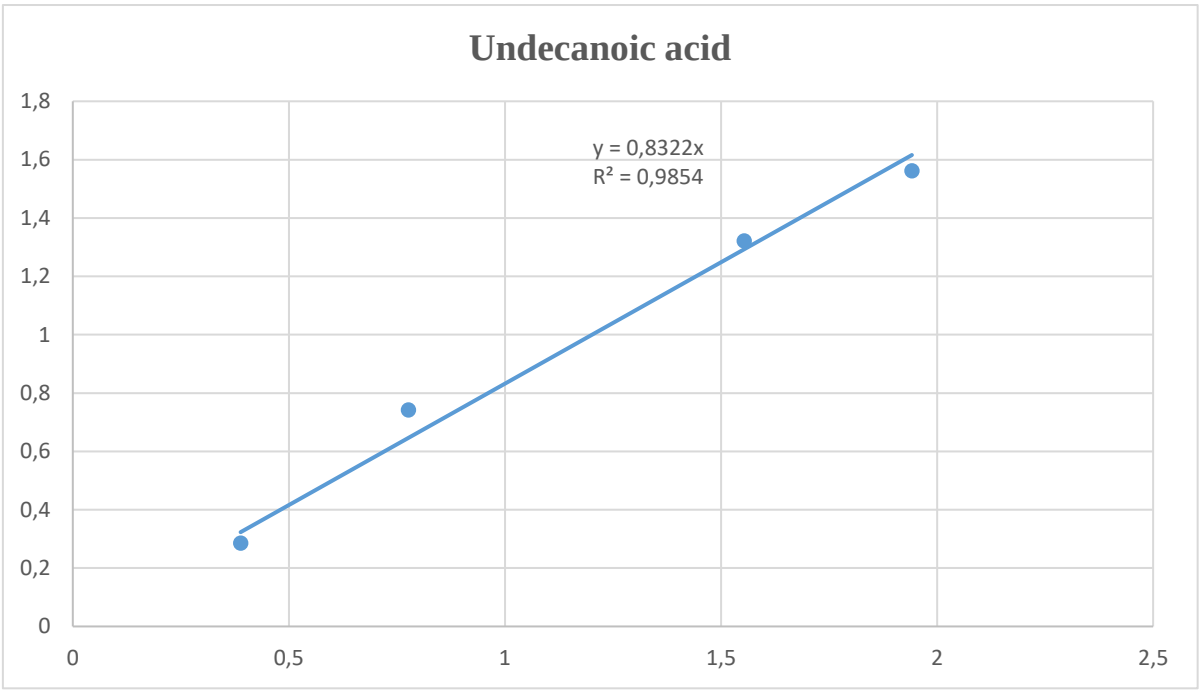


Figure E26: Calibration curve for compound **17.**